(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 February 2001 (08.02.2001)

PCT

(10) International Publication Number
WO 01/09094 A2

(51) International Patent Classification[7]: C07D 211/52, A61K 31/497, 31/4523, A61P 29/00, C07D 405/06, 493/04, 409/06, 495/04, 491/04, 401/06, 401/14, 471/04, 519/00, 313/12 // (C07D 493/04, 317:00, 313:00) (C07D 495/04, 333:00, 313:00) (C07D 491/04, 313:00, 221:00) (C07D 471/04, 223:00, 221:00) (C07D 495/04, 335:00, 221:00) (C07D 519/00, 491:00, 471:00) (C07D 519/00, 491:00, 491:00)

(21) International Application Number: PCT/US00/20607

(22) International Filing Date: 28 July 2000 (28.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/362,807 28 July 1999 (28.07.1999) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 09/362,907 (CIP)
Filed on 28 July 1999 (28.07.1999)

(71) Applicants (*for all designated States except US*): MILLENNIUM PHARMACEUTICALS, INC. [US/US]; 75 Sidney Street, Cambridge, MA 02139 (US). KYOWA HAKKO KOGYO CO., LTD. [JP/JP]; 1-6-1, Ohtemachi, Chiyoda-ku, Tokyo 100-8185 (JP).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): LULY, Jay, R. [US/US]; 24 Damien Road, Wellesley, MA 02481 (US). NAKASATO, Yoshisuke [JP/JP]; 80-1, Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka 411 (JP). OHSHIMA, Etsuo [JP/JP]; 2-223, Edogawadai-Nishi, Nagareyama-shi, Chiba 270-0115 (JP). SONE, Hiroki [JP/JP]; 1188 Shimotogari, Nagizumi-cho, Sunto-gun, Shizuoka 411 (JP). KOTERA, Osamu [JP/JP]; 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka 411 (JP). HARRIMAN, Geraldine, C., B. [US/US]; 50 South Arnold Road, Charlestown, RI 02813 (US). CARSON, Kenneth, G. [US/US]; 21 Sterling Road, Needham, MA 02492 (US).

(74) Agents: CARROLL, Alice, O. et al.; Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02421 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

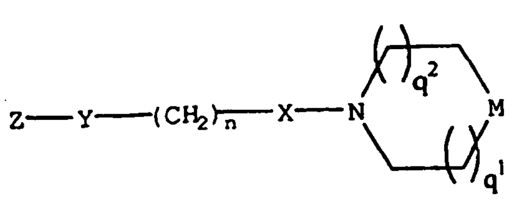
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/09094 A2

(54) Title: CHEMOKINE RECEPTOR ANTAGONISTS AND METHODS OF USE THEREFOR



(XXIV)

(57) Abstract: Disclosed are novel compounds and a method of treating a disease associated with aberrant leukocyte recruitment and/or activation. The method comprises administering to a subject in need an effective amount of a compound represented by structural formula (XXIV) or Z-Y-$(CH_2)_n$-X-$NR^{50}R^5$ and physiologically acceptable salts thereof.

AL 10

CHEMOKINE RECEPTOR ANTAGONISTS AND METHODS OF USE THEREFOR

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Serial No. 09/362,807, filed July 28, 1999, which is continuation-in-part of U.S. Serial No. 09/234,868, filed January 21, 1999, which is a continuation-in-part of U.S. Serial No. 09/148,515, filed September 4, 1998, which is a continuation-in-part of U.S. Serial No. 09/009,977, filed January 21, 1998, now abandoned; the entire teachings of each of the above-referenced applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Chemoattractant cytokines or chemokines are a family of proinflammatory mediators that promote recruitment and activation of multiple lineages of leukocytes and lymphocytes. They can be released by many kinds of tissue cells after activation. Continuous release of chemokines at sites of inflammation mediates the ongoing migration of effector cells in chronic inflammation. The chemokines characterized to date are related in primary structure. They share four conserved cysteines, which form disulfide bonds. Based upon this conserved cysteine motif, the family is divided into two main branches, designated as the C-X-C chemokines (α-chemokines), and the C-C chemokines (β-chemokines), in which the first two conserved cysteines are separated by an intervening residue, or adjacent

respectively (Baggiolini, M. and Dahinden, C. A., *Immunology Today*, *15*:127-133 (1994)).

The C-X-C chemokines include a number of potent chemoattractants and activators of neutrophils, such as interleukin 8 (IL-8), PF4 and neutrophil-activating peptide-2 (NAP-2). The C-C chemokines include RANTES (Regulated on Activation, Normal T Expressed and Secreted), the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β), eotaxin, and human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2, MCP-3), which have been characterized as chemoattractants and activators of monocytes or lymphocytes but do not appear to be chemoattractants for neutrophils. Chemokines, such as RANTES and MIP-1α, have been implicated in a wide range of human acute and chronic inflammatory diseases including respiratory diseases, such as asthma and allergic disorders.

The chemokine receptors are members of a superfamily of G protein-coupled receptors (GPCR) which share structural features that reflect a common mechanism of action of signal transduction (Gerard, C. and Gerard, N.P., *Annu Rev. Immunol.*, *12*:775-808 (1994); Gerard, C. and Gerard, N. P., *Curr. Opin. Immunol.*, *6*:140-145 (1994)). Conserved features include seven hydrophobic domains spanning the plasma membrane, which are connected by hydrophilic extracellular and intracellular loops. The majority of the primary sequence homology occurs in the hydrophobic transmembrane regions with the hydrophilic regions being more diverse. The first receptor for the C-C chemokines that was cloned and expressed binds the chemokines MIP-1α and RANTES. Accordingly, this MIP-1α/RANTES receptor was designated C-C chemokine receptor 1 (also referred to as CCR-1; Neote, K., *et al.*, *Cell*, *72*:415-425 (1993); Horuk, R. *et al.*, WO 94/11504, May 26, 1994; Gao, J.-I. *et al.*, *J. Exp. Med.*, *177*:1421-1427 (1993)). Three receptors have been characterized which bind and/or signal in response to RANTES: CCR3 mediates binding and

signaling of chemokines including eotaxin, RANTES, and MCP-3 (Ponath et al., *J. Exp. Med.*, *183*:2437 (1996)), CCR4 binds chemokines including RANTES, MIP-1α, and MCP-1 (Power, et al., *J. Biol. Chem.*, *270*:19495 (1995)), and CCR5 binds chemokines including MIP-1α, RANTES, and MIP-1β (Samson, *et al.*, *Biochem.* *35*: 3362-3367 (1996)). RANTES is a chemotactic chemokine for a variety of cell types, including monocytes, eosinophils, and a subset of T-cells. The responses of these different cells may not all be mediated by the same receptor, and it is possible that the receptors CCR1, CCR4 and CCR5 will show some selectivity in receptor distribution and function between leukocyte types, as has already been shown for CCR3 (Ponath *et al.*). In particular, the ability of RANTES to induce the directed migration of monocytes and a memory population of circulating T-cells (Schall, T. et al., *Nature*, *347*:669-71 (1990)) suggests this chemokine and its receptor(s) may play a critical role in chronic inflammatory diseases, since these diseases are characterized by destructive infiltrates of T cells and monocytes.

Many existing drugs have been developed as antagonists of the receptors for biogenic amines, for example, as antagonists of the dopamine and histamine receptors. No successful antagonists have yet been developed to the receptors for the larger proteins such as chemokines and C5a. Small molecule antagonists of the interaction between C-C chemokine receptors and their ligands, including RANTES and MIP-1α, would provide compounds useful for inhibiting harmful inflammatory processes "triggered" by receptor ligand interaction, as well as valuable tools for the investigation of receptor-ligand interactions.

SUMMARY OF THE INVENTION

It has now been found that a class of small organic molecules are antagonists of chemokine receptor function and can inhibit leukocyte activation and/or recruitment. An

antagonist of chemokine receptor function is a molecule which can inhibit the binding and/or activation of one or more chemokines, including C-C chemokines such as RANTES, MIP-1α, MCP-2, MCP-3 and/or MCP-4 to one or more chemokine receptors on leukocytes and/or other cell types. As a consequence, processes and cellular responses mediated by chemokine receptors can be inhibited with these small organic molecules. Based on this discovery, a method of treating a subject with a disease associated with aberrant leukocyte recruitment and/or activation is disclosed as well as a method of treating a disease mediated by chemokine receptor function. The method comprises administering to a subject in need of treatment an effective amount of a compound or small organic molecule which is an antagonist of chemokine receptor function. Compounds or small organic molecules which have been identified as antagonists of chemokine receptor function are discussed in detail herein below, and can be used for the manufacture of a medicament for treating or for preventing a disease associated with aberrant leukocyte recruitment and/or activation. The invention also relates to the disclosed compounds and small organic molecules for use in treating or preventing a disease associated with aberrant leukocyte recruitment and/or activation. The invention also includes pharmaceutical compositions comprising one or more of the compounds or small organic molecules which have been identified herein as antagonists of chemokine function and a suitable pharmaceutical carrier. The invention further relates to novel compounds which can be used to treat an individual with a disease associated with aberrant leukocyte recruitment and/or activation and methods for their preparation.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic showing the preparation of the compounds represented by Structural Formulas (I) and (II).

Figure 2 is a schematic showing the preparation of representative compounds Structural Formula (I) and (II),

wherein Z is represented by Structural Formulas (IV) and wherein Ring A and/or Ring B in Z can be substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$.

Figure 3 is a schematic showing the preparation of the compounds represented by Structural Formula (I) and (II), wherein Z is represented by Structural Formulas (VIII) and (XIII)-(XVIc) and wherein V is W_a.

Figure 4 is a schematic showing the preparation of compounds represented by Structural Formulas (I) and (II), wherein Z is represented by Structural Formula (IV), wherein W is H.

Figure 5 is a schematic showing the preparation of compounds represented by Structural Formulas (I) and (II), wherein Z is represented by Structural Formula (IV), wherein W is H.

Figures 6A-6AD show the structures of a number of exemplary compounds of the present invention.

Figure 7 shows the preparation of compounds represented by Structural Formula (I), where in Z is represented by Structural Formulas (VI) and wherein Ring A and/or Ring B in Z is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$,u is one.

Figure 8A shows the preparation of compounds represented by Structural Formula (I), wherein Z is represented by Structural Formulas (VI) and wherein Ring A or Ring B in Z is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, u is zero.

Figure 8B is a schematic showing the preparation of 4-(4-chlorophenyl)-4-fluoropiperidine.

Figure 8C is a schematic showing the preparation of 4-4-azido-4-(4-chlorophenyl)piperidine.

Figure 8D is a schematic showing the preparation of 4-(4-chlorophenyl)-4-methylpiperidine.

Figure 9A is a schematic showing the preparation of compounds represented by Structural Formulas (I), (VIII) and (VIII) wherein R^1 is an amine.

Figure 9B is a schematic showing the preparation of compounds represented by Structural Formulas (I), (VIII) and (VIII) wherein R^1 is an alkylamine.

Figure 9C is a schematic showing the preparation of 2-(4-chlorophenyl)-1-(*N*-methyl)ethylamine.

Figure 9D is a schematic showing the preparation of 3-(4-chlorophenyl)-3-chloro-1-hydroxypropane.

Figure 9E is a schematic showing the preparation of 3-(4-chlorophenyl)-1-*N*-methylaminopropane.

Figure 10A is a schematic showing the preparation of 3-(4-chlorophenyl)-3-hydroxyl-3-methyl-1-*N*-methylaminopropane.

Figure 10B is a schematic showing the preparation of 1-(4-chlorobenzoyl)-1,3-propylenediamine.

Figure 10C is a schematic showing three procedures for the preparation of compounds represented by Structural Formulas (I),(XXIV), (XXV), (XXVI) and (XXVII) wherein Z is represented by Structural Formula (XVII) and wherein Ring A or Ring B in Z is substituted with R^{40}. In Figure 10C, R^{40} is represented by $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, u is one, t is zero.

Figure 10D is a schematic showing the preparation of 4-(4-chlorophenyl)-4-pyridine.

Figures 11A-11K show the structures of exemplary compounds of the present invention.

Figure 12 is a schematic showing the preparation of compounds of formula (XV-b).

Figure 13 is a schematic showing the preparation of compounds of formula (XV-c).

Figure 14 is a schematic showing the preparation of compounds of formula (XV-e).

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to small molecule compounds which are modulators of chemokine receptor function. In a preferred embodiment, the small molecule compounds are antagonists of chemokine receptor function. Accordingly,

processes or cellular responses mediated by the binding of a chemokine to a receptor can be inhibited (reduced or prevented, in whole or in part), including leukocyte migration, integrin activation, transient increases in the concentration of intracellular free calcium $[Ca^{++}]_i$, and/or granule release of proinflammatory mediators.

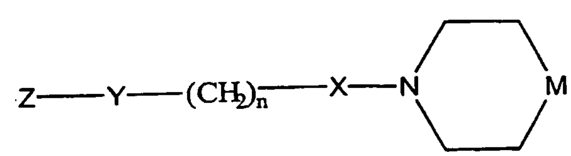
The invention further relates to a method of treatment, including prophylactic and therapeutic treatments, of a disease associated with aberrant leukocyte recruitment and/or activation or mediated by chemokines or chemokine receptor function, including chronic inflammatory disorders characterized by the presence of RANTES, MIP-1α, MCP-2, MCP-3 and/or MCP-4 responsive T cells, monocytes and/or eosinophils, including but not limited to diseases such as arthritis (e.g., rheumatoid arthritis), atherosclerosis, arteriosclerosis, restenosis, ischemia/reperfusion injury, diabetes mellitus (e.g., type 1 diabetes mellitus), psoriasis, multiple sclerosis, inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, rejection of transplanted organs and tissues (i.e., acute allograft rejection, chronic allograft rejection), graft versus host disease, as well as allergies and asthma. Other diseases associated with aberrant leukocyte recruitment and/or activation which can be treated (including prophylactic treatments) with the methods disclosed herein are inflammatory diseases associated with Human Immunodeficiency Virus (HIV) infection, e.g., AIDS associated encephalitis, AIDS related maculopapular skin eruption, AIDS related interstitial pneumonia, AIDS related enteropathy, AIDS related periportal hepatic inflammation and AIDS related glomerulo nephritis. The method comprises administering to the subject in need of treatment an effective amount of a compound (i.e., one or more compounds) which inhibits chemokine receptor function, inhibits the binding of a chemokine to leukocytes and/or other cell types, and/or which inhibits leukocyte migration to, and/or activation at, sites of inflammation.

The invention further relates to methods of antagonizing a chemokine receptor, such as CCR1, in a mammal comprising administering to the mammal a compound as described herein.

According to the method, chemokine-mediated chemotaxis and/or activation of pro-inflammatory cells bearing receptors for chemokines can be inhibited. As used herein, "pro-inflammatory cells" includes but is not limited to leukocytes, since chemokine receptors can be expressed on other cell types, such as neurons and epithelial cells.

While not wishing to be bound by any particular theory or mechanism, it is believed that compounds of the invention are antagonists of the chemokine receptor CCR1, and that therapeutic benefits derived from the method of the invention are the result of antagonism of CCR1 function. Thus, the method and compounds of the invention can be used to treat a medical condition involving cells which express CCR1 on their surface and which respond to signals transduced through CCR1, as well as the specific conditions recited above.

In one embodiment of the present invention, the antagonist of chemokine receptor function is represented by Structural Formula (I):



(I)

Z is a cycloalkyl or non-aromatic heterocyclic ring fused to one or more carbocyclic aromatic rings and/or heteroaromatic rings.

Y is a covalent bond, -O-, -CO- or =CH-.

n is an integer, such as an integer from one to about five. n is preferably one, two, or three. In alternative

embodiments, other aliphatic or aromatic spacer groups (L) can be employed for $(CH_2)_n$.

X is a covalent bond or -CO-.

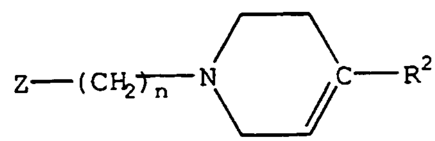
M is $>NR^2$ or $>CR^1R^2$. Preferably, M is $>C(OH)R^2$.

R^1 is -H, -OH, $-N_3$, a halogen, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -COOH, -CN, $-CO-NR^3R^4$, $-NR^3R^4$; or R^1 can be a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M. R^1 is preferably -H or -OH.

R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, -O-(substituted or unsubstituted aromatic group) or -O-(substituted or unsubstituted aliphatic group). R^2 is preferably an aromatic group or a substituted aromatic group.

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group. R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, can alternatively form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

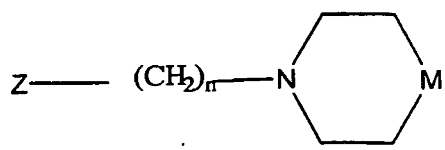
In embodiments where M is $>CR^1R^2$ and R^1 is a covalent bond between the carbon atom at M and an adjacent carbon atom in the ring which contains M, the antagonist of chemokine function can be represented by Structural Formula (Ia).



(Ia)

Z, n, and R^2 are as described in Structural Formula (I).

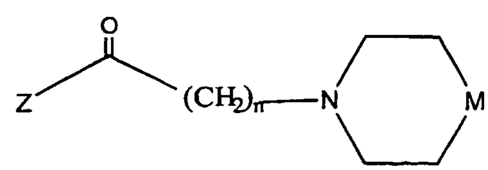
In a preferred embodiment, -X- and -Y- in Structural Formula (I) are each a covalent bond and the antagonist of chemokine receptor function is a compound represented by Structural Formula (II):



(II)

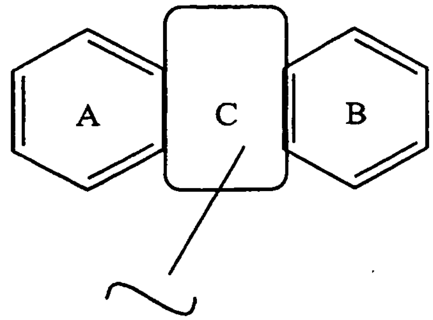
Z, n and M are as described above for Structural Formula (I).

In another preferred embodiment, -X- is a covalent bond, -Y- is -CO- and the antagonist of chemokine receptor function is a compound represented by Structural Formula (III):



(III)

Preferably, Z is a tricyclic ring system comprising two carbocyclic aromatic groups fused to a five, six, seven or eight membered cycloalkyl group or to a non-aromatic heterocyclic ring. In one example, Z is represented by Structural Formula (IV):



(IV)

The phenyl rings in Structural Formula (IV), labeled with an "A" and "B", are referred to herein as "Ring A" and "Ring B", respectively. The central ring, labeled with a "C', is referred to as "Ring C" and can be, for example, a five, six, seven or eight membered non-aromatic carbocyclic ring (e.g., a cycloheptane or cyclooctane ring) or a non-aromatic heterocyclic ring. When Ring C is a non-aromatic heterocyclic ring, it can contain one or two heteroatoms such as nitrogen, sulfur or oxygen. When Z is represented by Structural Formula (IV), the tricyclic ring system can be connected to Y in Structural Formula (I) by a single covalent bond between Y and a ring atom in Ring C.

Ring A and/or Ring B can be unsubstituted. Alternatively, Ring A and/or Ring B can have one or more substituents. Suitable substituents are as described herein below for aromatic groups. In one example, Ring A or Ring B is substituted with $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}-$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$.

u is zero or one.

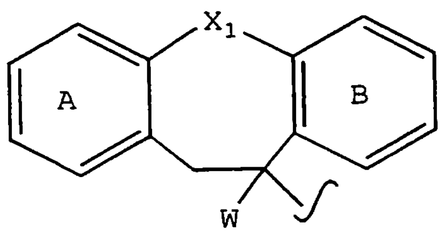
t is an integer, such as an integer from zero to about three, and the methylene group, $-(CH_2)_t-$, can be substituted, as described herein for aliphatic groups, or unsubstituted.

R^{20}, R^{21} or R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group. Alternatively, R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, can form a non-aromatic heterocyclic ring.

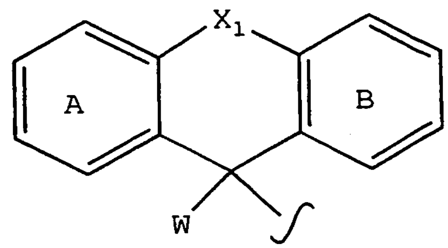
Ring C optionally contains one or more substituents as described herein below. Preferably, Ring C is unsubstituted or substituted with an electron withdrawing group. Suitable electron withdrawing groups include -CN, $-CH_2=NH$, alkylimines, alkylsulfonyl, carboxamido, carboxylic alkyl esters, $-NO_2$ and halogens (e.g., -Br and -Cl). Alternatively, Ring C is substituted with a group selected from $-CH_2-NR^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$.

R^{11} and R^{12} are independently -H, an aliphatic group a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group. Alternatively, R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring.

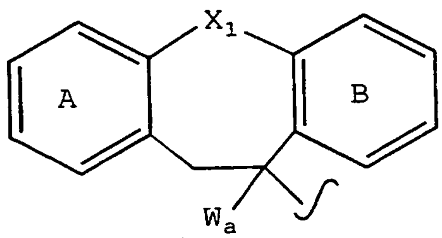
Examples of suitable tricyclic rings systems represented by Structural Formula (IV) are provided by Structural Formula (V)-(VIII), shown below:



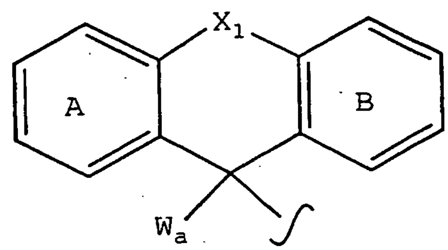
(V)



(VI)



(VII)



(VIII

X_1 is a covalent bond, -S-, $-CH_2-$ or $-CH_2-S-$. Preferably, X_1 is -S- in Structural Formulas (V) and (VII). Preferably, X_1 is $-CH_2-S-$ in Structural Formulas (VI) and (VIII).

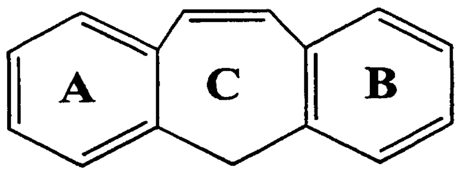
W is -H or an electron withdrawing group, as described above for Structural Formula (IV). A preferred electron withdrawing group is -CN.

W_a is a group selected from $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$.

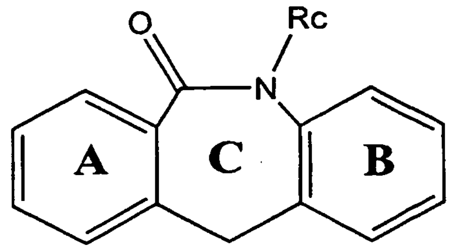
R^{11} and R^{12} are as defined in Structural Formula (IV).

Ring A and Ring B in Structural Formulas (V)-(VIII) can be as described above in Structural Formula (IV).

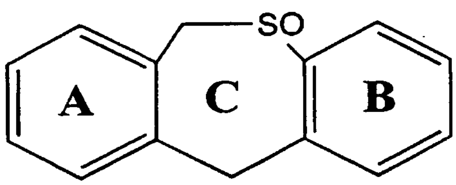
Other examples of suitable tricyclic ring systems represented by Structural Formula (IV) are shown below in Structural Formulas (XI),(XII), (XIIa), (XIIb) and (XIIc):



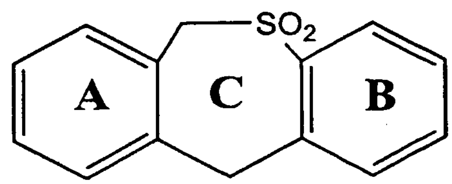
(XI)



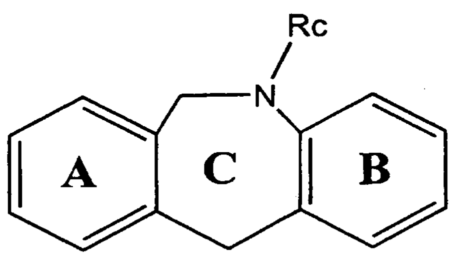
(XII)



(XIIa)



(XIIb)



(XIIc)

Rings A-C in Structural Formulas (XI)-(XII), (XIIa), (XIIb) and (XIIc) can be as described for Structural Formula (IV).

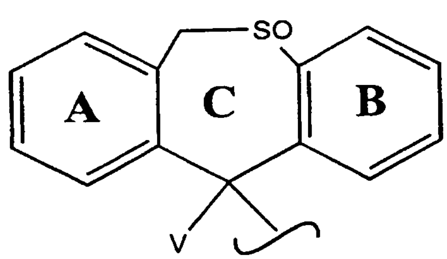
R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group.

Preferably, R_c is a substituted C_1-C_{20} aliphatic group, a C_1-C_{20} aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group. In one example, R_c is $-(CH_2)_s$-$COOR^{30}$, $-(CH_2)_s$-$OC(O)R^{30}$, $-(CH_2)_s$-$C(O)$-$NR^{31}R^{32}$ or $-(CH_2)_s$-$NHC(O)$-O-R^{30}.

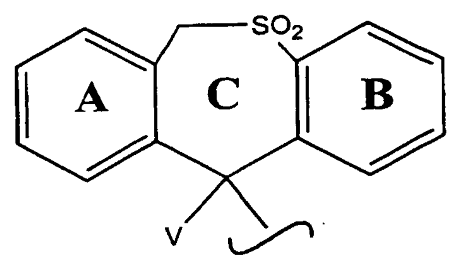
s is an integer from one to about three.

R^{30}, R^{31}, and R^{32} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a substituted or unsubstituted non-aromatic heterocyclic group. Alternatively, R^{31} and R^{32}, taken together with the nitrogen atom to which they are bonded, can form a non-aromatic heterocyclic ring.

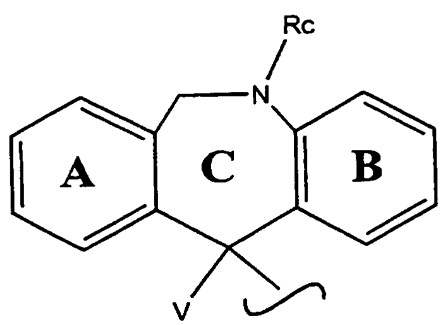
Preferred examples of tricyclic ring systems represented by Structural Formulas (XI)-(XII), (XIIa), (XIIb) and (XIIc) are shown below in Structural Formulas (XIII)-(XVI), (XVIa), (XVIb) and (XVIc):



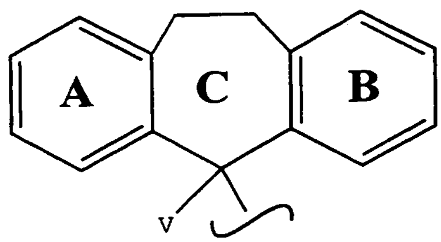
(XVIa)



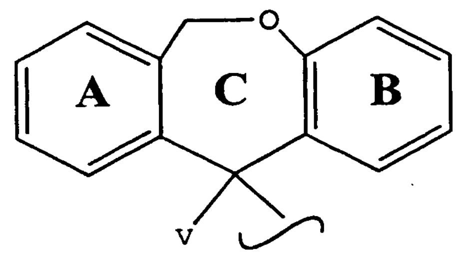
(XVIb)



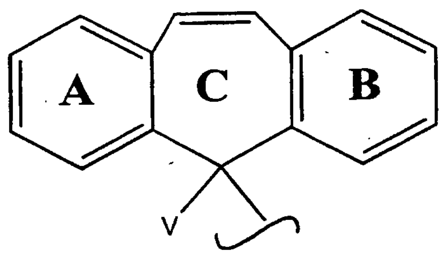
(XVIc)



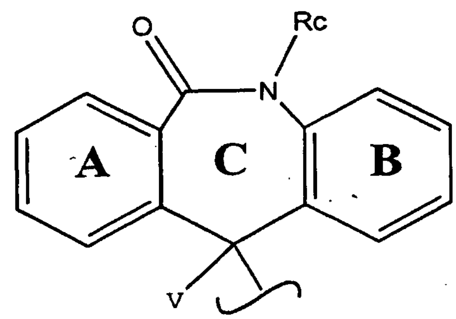
(XIII)



(XIV



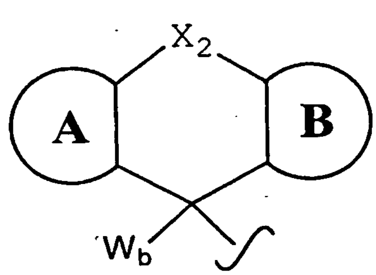
(XV)



(XVI)

V can be W or W_a, which are as described above for Structural Formula (V)-(VIII).

In another preferred embodiment, Z is a tricyclic ring system comprising one or more aromatic groups (i.e., heteroaryl or aromatic carbocyclic) fused to a six, seven or eight membered cycloalkyl group or to a non-aromatic heterocyclic ring. Examples are represented by Structural Formula (XVII):



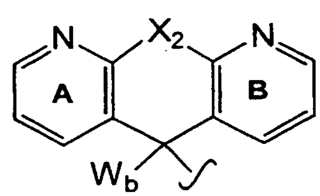
(XVII)

wherein X_2 is -O-, a bond, -S-CH_2-, -CH_2-S-, -CH_2-O-, -O-CH_2-, -CO-NR_c-, -NR_c-CO-, -CH_2-S(O)$_2$-, -S(O)$_2$-CH_2-, -CH_2-NR_c-, -Nr_c-CH_2-, -CH_2-CH_2-, -CH=CH-, -CH_2-SO-, -SO-CH_2-.

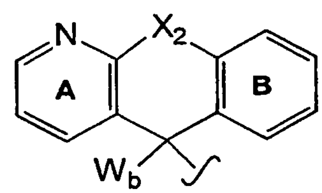
W_b is -H, -CH=NH, -CN, -CH_2-$NR^{11}R^{12}$, -CH_2-OR^{11}, -CH_2-NH-CO-$NR^{11}R^{12}$, -CH_2-O-CO-$NR^{11}R^{12}$ or -CH_2-NHC(O)-O-R^{11}. R^{11} and R^{12} are as defined above for Structural Formula (IV).

Ring A and Ring B in Structural Formulas (XVII) are independently substituted or unsubstituted aromatic groups.

In one example, Ring A is a substituted or unsubstituted heteroaryl group and Ring B is a substituted or unsubstituted aromatic carbocyclic group. In another example Ring A and Ring B are independently substituted or unsubstituted heteroaryl groups. In another example, Ring A and Ring B are both, independently, a substituted or unsubstituted phenyl group. In yet another example Ring A is a substituted or unsubstituted heteroaryl group, preferably a pyridyl group, and Ring B is a substituted or unsubstituted phenyl group. Suitable tricyclic rings Z can be represented, for example, by Structural Formulas (XVIIa) and (XVIIb):



(XVIIa)

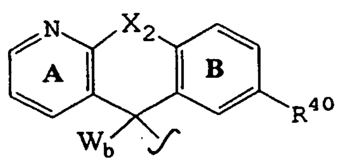


(XVIIb)

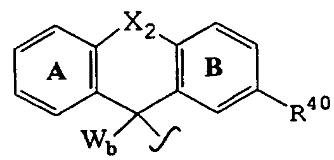
Ring A and/or Ring B can be substituted with R^{40}, which is a substituent as described herein for an aromatic group.

In a preferred embodiment, Ring A is a pyridyl group, Ring B is a phenyl group and Ring B is substituted para to the carbon atom in Ring B that is also bonded to X_2 in Ring C.

In another preferred embodiment, Ring A is a phenyl group, Ring B is a phenyl group and Ring B is substituted para to the carbon atom in Ring B that is also bonded to X_2 in Ring C. The Z groups of these embodiments can be represented by Structural Formulas (XVIIIa)and (XVIIIb):



(XVIIIa)



(XVIIIb)

X_2 is as described in Structural Formula (XVII). Preferably, X_2 is $-CH_2-O-$, $-CH_2-CH_2-$ or $-CH_2-S-$. W_b is as defined herein.

In one embodiment, R^{40} is -OH, -COOH, $-NO_2$, a halogen, an aliphatic group, a substituted aliphatic group, $-NR^{24}R^{25}$, $-CONR^{24}R^{25}$, $-C(=NR^{60})NR^{21}R^{22}$, an aromatic group, a substituted aromatic group, -Q-(aliphatic group), -Q-(substituted aliphatic group), -O-(aliphatic group), -O-(substituted aliphatic group),-O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$. Q, R^{20}, R^{21}, R^{22}, R^{24}, R^{25}, R^{60}, u and t are as described herein.

Preferably, R^{40} is an aliphatic group, substituted aliphatic group, -O-(aliphatic group) or -O-(substituted aliphatic group). More preferably, R^{40} is -O-alkyl, such as $-O-CH_3$, $-O-C_2H_5$, $-O-C_3H_7$ or $-O-C_4H_9$.

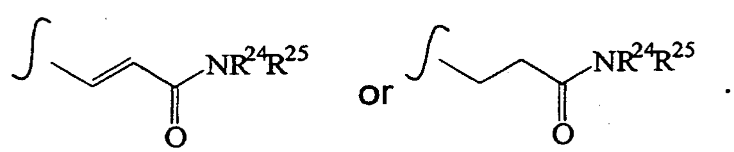
In another embodiment, R^{40} can be represented by $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, wherein u is one, t is zero, and R^{21} and R^{22} are as described herein. In this embodiment, R^{21} and R^{22} can each independently be -H, a substituted or unsubstituted aliphatic group, a substituted or unsubstituted

aromatic group, or R^{21} and R^{22} taken together with the nitrogen atom to which they are bonded form a substituted or unsubstituted nonaromatic heterocyclic ring (e.g., pyrrolidine, piperidine, morpholine).

In another embodiment, R^{40} can be represented by $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, wherein u is zero, t is one to about three, and R^{21} and R^{22} are as described herein.

In another embodiment, R^{40} can be represented by $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, wherein both u and t are zero, and R^{21} and R^{22} are as described herein.

In another embodiment, R^{40} is an aliphatic group (e.g., methyl, ethyl, propyl) that is substituted with $-NR^{24}R^{25}$ or $-CONR^{24}R^{25}$, wherein R^{24} and R^{25} are as described herein. For example, R^{40} can be represented by

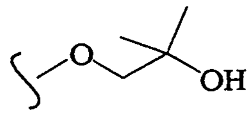


In another embodiment, R^{40} is $-O-C(O)-NR^{21}R^{26}$, wherein R^{21} is as described herein, R^{26} can be -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), $-S(O)_2-$(substituted or unsubstituted aliphatic group), $-S(O)_2-$(substituted or unsubstituted aromatic group) or R^{21} and R^{26}, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

In additional embodiments, R^{40} can be $-S(O)_2-NR^{21}R^{22}$ or $-N-C(O)-NR^{21}R^{22}$, wherein R^{21} and R^{22} are as described herein.

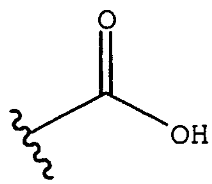
In a preferred embodiment, the chemokine receptor antagonist can be represented by Structural Formula I wherein n is three, M is $C(OH)R^2$, R^2 is a phenyl group or a halophenyl group (e.g., 4-chlorophenyl) and Z is represented by

Structural Formula (XVIIIa) or (XVIIIb) wherein X_2 is $-CH_2-O-$. In one example of this embodiment, R^{40} can be -O-(substituted aliphatic group), such as

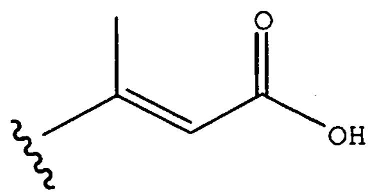


.

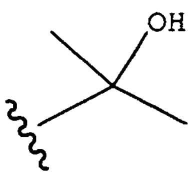
In particularly preferred embodiments, R^{40} is



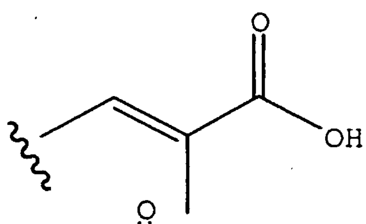
,



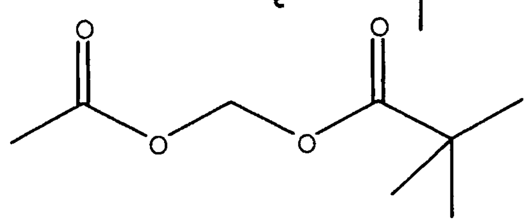
,



,

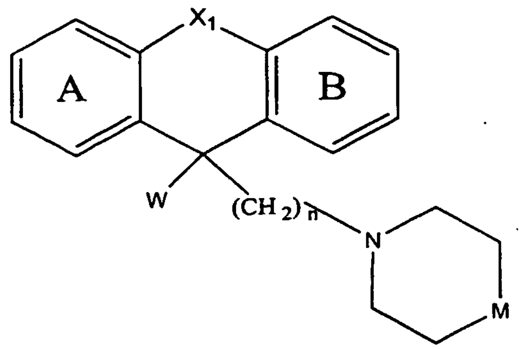


or

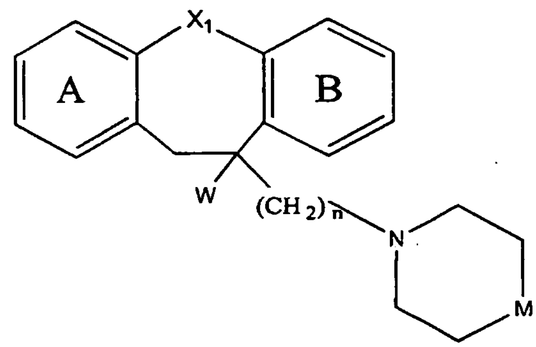


.

In yet another preferred embodiment, the antagonist of chemokine function is a compound represented by Structural Formula (XXII) and (XXIII):



(XXII)

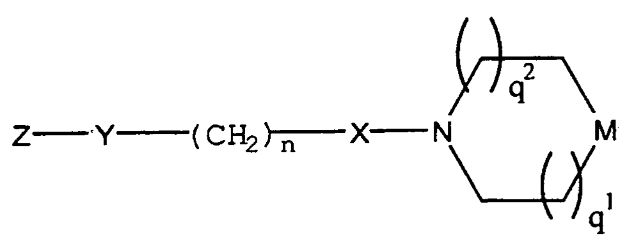


(XXIII)

In Structural Formulas (XXII) and (XXIII), X_1 can be as defined above for Structural Formulas (V) and (VI); n is an integer from two to five; W can be -H, -CN, -CH=NH, an electron withdrawing group, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$.

In Structural Formulas (XXII) and (XXIII), Ring A can be substituted with R^8 and R^9, wherein R^8 and R^9 are independently -H, a halogen, alkoxy or alkyl, or, taken together with Ring A, form a naphthyl group. M is >N(alkanoyl), >N(aroyl), >N(aralkoyl), >N(alkyl), >N(aralkyl), >N(cycloalkyl), >C(OH)(aryl) or >CH(heteroaryl).

In another embodiment, the antagonist of chemokine activity can be represented by Structural Formula (XXIV):



(XXIV)

and physiologically acceptable salts thereof.

n, Y and X are as described in Structural Formula (I).

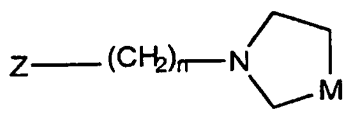
M is $>NR^2$, $>CR^1R^2$, $-O-CR^1R^2-O-$ or $-CH_2-CR^1R^2-O-$.

R^1 and R^2 are as described in Structural Formula (I).

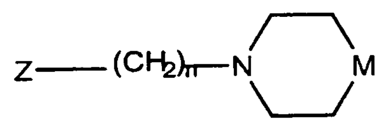
Z is as described in Structural Formulas (IV)

-(VIII) and/or (XI)-(XVII), (XVIIIa) or (XVIIIb). Preferably, Z is as described in Structural Formula (XVIIIa) or (XVIIIb).

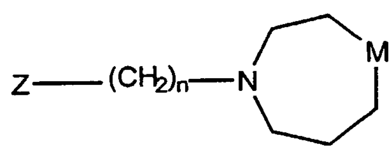
q^1 is an integer, such as an integer from zero to about three, and q^2 is an integer from zero to about one. The ring containing M can be substituted or unsubstituted. Thus, the antagonist of chemokine function can be represent by, for example, Structural Formulas (XXIVa)-(XXIVk):



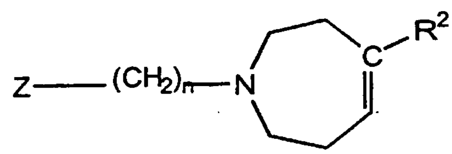
(XXIVa)



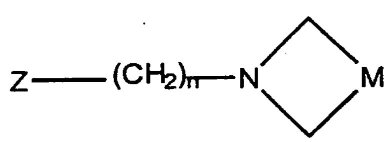
(XXIVb



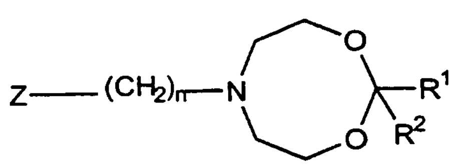
(XXIVc)



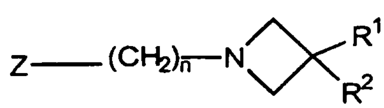
(XXIVd)



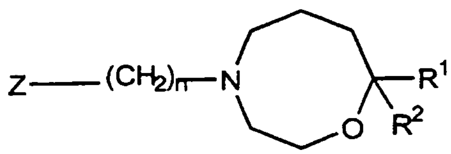
(XXIVe



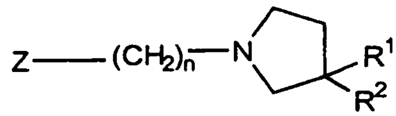
(XXIVf)



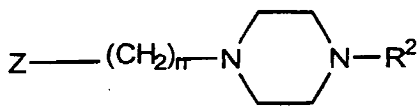
(XXIVg)



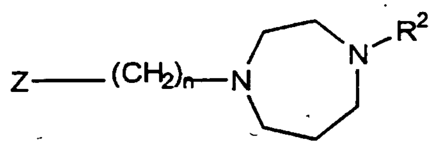
(XXIVh)



(XXIVi)



(XXIVj)



(XXIVk)

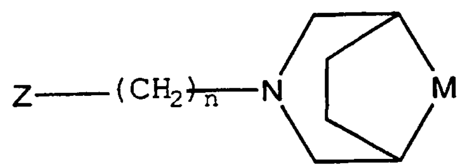
and physiologically acceptable salts thereof, wherein Z, n and M are as described in Structural Formula (XXIV), and the ring which contains M is substituted or unsubstituted. The ring containing M can have one or more suitable substituents which are the same or different. Suitable substituents for the ring which contains M and other nonaromatic heterocyclic rings are as described herein. For example, the ring containing M can be substituted with a methyl, ethyl, propyl, butyl or oxo group.

The nitrogen atom in the ring containing M can be a tertiary nitrogen as depicted in Structural Formula (IV), or the nitrogen atom can be quaternized with a suitable substituent, such as a C_1 to about C_6 or a C_1 to about C_3 substituted or unsubstituted aliphatic group. Compounds which comprise a quaternary nitrogen atom can also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like.

The antagonist of chemokine function can be represented by Structural Formula (XXIV) wherein the heterocyclic ring containing M is substituted with a suitable bivalent group which is bonded to two atoms that are in the ring, thereby

forming a bicyclic moiety. Suitable bivalent groups include, for example, substituted or unsubstituted bivalent aliphatic groups, such as a C_1-C_6 alkylene group.

The antagonist of chemokine receptor function can comprise a variety of bicyclic moieties. In one embodiment, the antagonist of chemokine receptor function can be represented by Structural Formula (XXV):



(XXV)

and physiologically acceptable salts thereof.

M is $>NR^2$, $>CR^1R^2$, $-O-CR^1R^2-O-$ or $-CH_2-CR^1R^2-O-$. Preferably, M is $>NR^2$ or $>CR^1R^2$. R^1, R^2 and n are as described in Structural Formula (I), and Z are as described herein. Preferably, Z is as described in Structural Formula (XVIIIa) or (XVIIIb).

In another embodiment, the antagonist of chemokine receptor function is represented by Structural Formula (XXVI):

$$Z{-}Y{-}(CH_2)_n{-}X{-}NR^{50}R^{51}$$

(XXVI

and physiologically acceptable salts thereof.

Z is as described herein, preferably as described in Structural Formula (XVIIIa) or (XVIIIb).

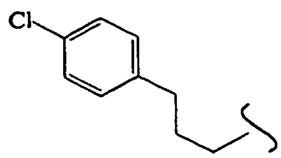
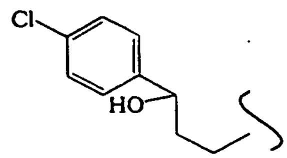
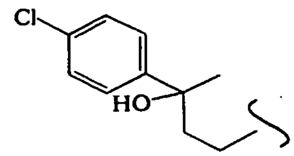
n is an integer, such as an integer from one to about four. Preferably, n is one, two or three. More preferably n is two. In alternative embodiments, other aliphatic or aromatic spacer groups (L) can be employed for $(CH_2)_n$.

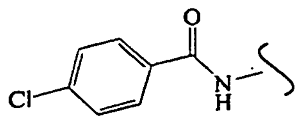
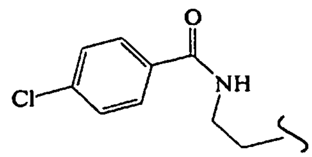
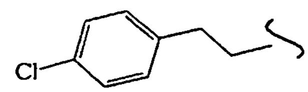
R^{50} and R^{51} are each independently -H, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, $-NR^3R^4$, an aromatic group, a substituted aromatic group, a benzyl group,

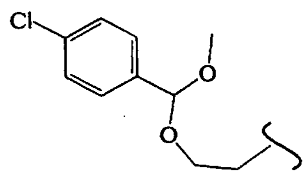
a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group or a covalent bond between the nitrogen atom an adjacent carbon atom.

R^3 and R^4 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group. R^3 and R^4 taken together with the atom to which they are bonded, can alternatively form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

In a preferred embodiment R^{50} is a substituted aliphatic group, such as a substituted C_1 to about C_{12} alkyl group, and R^{51} is -H or a substitited or unsubstituted aliphatic group. More preferably, R^{50} is a substituted linear or branched C_2 to about C_7 aliphatic group wherein one or more carbon atoms can be replaced by a heteroatom, such as nitrogen, oxygen or sulfur, and R^{51} is -H or a linear or branched C_1 to about C_6 or a C_1 to about C_3 aliphatic group wherein one or more carbon atoms can be replaced by a heteroatom. R^{50} and R^{51} can be substituted with one or more suitable substituents, as described herein, preferably with an aromatic group (e.g., phenyl, 4-halophenyl). For example, R^{50} can be selected from the group consisting of:

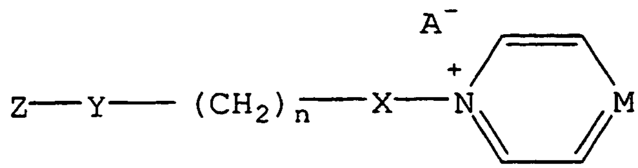
,
,
,

,
,
 and

.

The activity of chemokine receptor antagonists represented by Structural Formula XXVI can be affected by the character of the nitrogen atom to which R^{50} and R^{51} are bonded. It is believed that compounds in which said nitrogen atom is basic can have potent chemokine receptor antagonist activity. It is known that the basicity of a nitrogen atom can be decreased when the nitrogen atom is bonded to a carbonyl group, sulfonyl group or a sulfinyl group. Therefore, it is preferred that neither R^{50} nor R^{51} comprise a carbonyl group, sulfonyl group or sulfinyl group that is directly bonded to the nitrogen atom.

In another aspect, the antagonist of chemokine receptor function is represented by Structural Formula (XXVII):



and physiologically acceptable salts thereof.

n, Y and X are as described in Structural Formula (I).

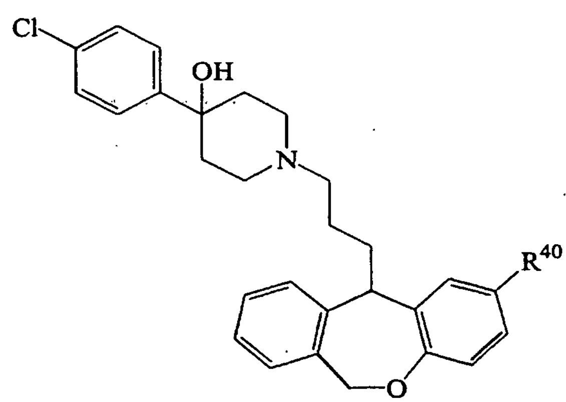
M is $>NR^2$ or $>CR^2$.

R^2 is as described in Structural Formula (I).

Z is as described in Structural Formulas (IV) -(VIII) and/or (XI)-(XVII), (XVIIIa) or (XVIIIb). Preferably, Z is as described in Structural Formula (XVIIIa) or (XVIIIb).

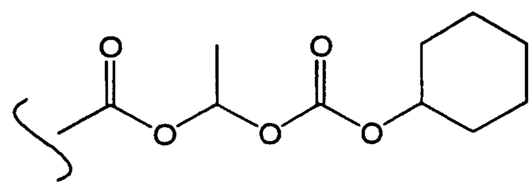
A^- is a physiologically acceptable anion. Preferably, A^- is Cl^- or Br^-.

The chemokine receptor antagonist described herein can be prepared and administered as active compounds or as prodrugs. Generally, prodrugs are analogues of pharmaceutical agents which can undergo chemical conversion by metabolic processes to become fully active. For example, A prodrug of the invention can be prepared by selecting appropriate groups for R^{40}. In one embodiment, a prodrug can be represented by Structural Formula (XXVIII):



(XXVIII)

wherein, R^{40} is Q-substituted aliphatic group, and the aliphatic group is substituted with $-(O)_u-(CH_2)_t-C(O)OR^{20}$, wherein Q is -C(O)O-, u is one, t is zero and R^{20} is a cyclic aliphatic group. For example, when the substituted aliphatic group is a substituted ethyl group, R^{40} can be represented by:



Such a prodrug can be converted to an active chemokine receptor antagonist represented by Structural Formula (XXVIII), wherein R^{40} is -COOH.

Another embodiment of the invention provides novel compounds employed in these methods.

Also included in the present invention are physiologically acceptable salts of the compounds represented by Structural Formulas (I) through (XXVIII). Salts of compounds containing an amine or other basic group can be obtained, for example, by reacting with a suitable organic or inorganic acid, such as hydrogen chloride, hydrogen bromide, acetic acid, citric acid, perchloric acid and the like. Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Salts of compounds containing a carboxylic acid or other acidic functional group can be prepared by reacting with a suitable base, for example, a hydroxide base. Salts of acidic functional groups contain a countercation such as sodium, potassium, ammonium, calcium and the like.

As used herein, aliphatic groups include straight chained, branched or cyclic C_1-C_{20} hydrocarbons which are completely saturated or which contain one or more units of unsaturation. Preferred aliphatic groups are C_1 to about C_{10} hydrocarbons. More preferred are C_1 to about C_6 or C_1 to about

C_3 hydrocarbons. One or more carbon atoms in an aliphatic group can be replaced with a heteroatom, such as nitrogen, oxygen or sulfur. For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic C_1-C_{20} alkyl, alkenyl or alkynyl groups.

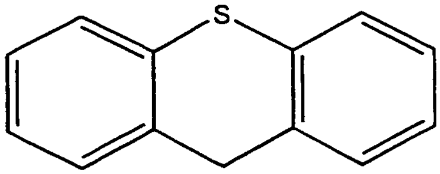
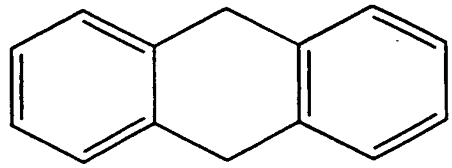
An aminoalkyl group is an alkyl group substituted with $-NR^{24}R^{25}$, R^{24} and R^{25} are as described herein. Preferably the alkyl moiety comprises one to about twelve, more preferably one to about six carbon atoms. The alkyl moiety of an aminoalkyl group can be unsubstituted or substituted as described herein for aliphatic groups. Examples of suitable aminoalkyl groups include aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, dimethylaminoethyl, diethylaminomethyl, methylaminohexyl, aminoethylenyl and the like.

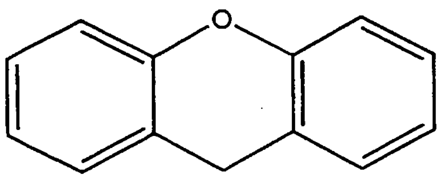
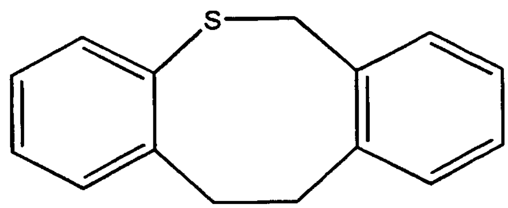
An "alkyl group" is a saturated aliphatic group, as defined above. The term "alkoxy" refers to an alkyl ether chain with an alkyl group. "Alkanoyl" refers to alkyl substituted carbonyl; "aralkanoyl" refers to phenyl-alkyl-CO- and "aroyl" refers to arylcarbonyl including benzoyl, naphthoyl and the like. The term "halogen" means fluoro, chloro, bromo and iodo. The term "substituted phenyl' means phenyl substituted by alkyl, halogen, alkoxy, nitro, amino, acetamido, cyano and trifluoromethyl and naphthyl. "Aralkyl" means $-(CH_2)_x$-aryl, wherein x is an integer from one to four including benzyl.

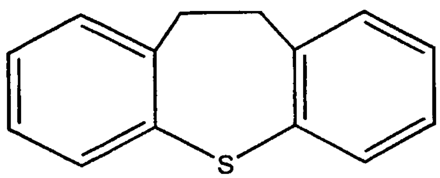
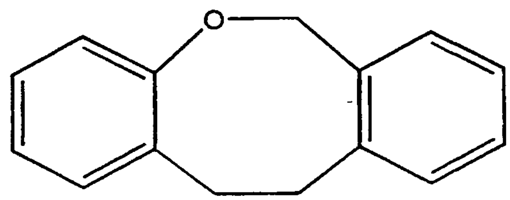
Aromatic groups include carbocyclic aromatic groups such as phenyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl, and heterocyclic aromatic or heteroaryl groups such as *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl,

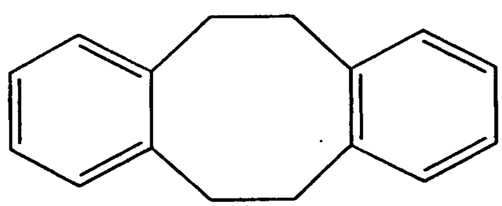
5-tetrazolyl, 2-oxazolyl, 4-oxazolyl and 5-oxazolyl. Where these rings are fused, for example, to Ring C, the stated point of attachment can be either of the two fused bonds.

Aromatic groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other rings. Examples include tetrahydronapthyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 3-indolyl, 2-quinolinyl, 3-quinolinyl, 2-benzothiazolyl, 2-benzooxazolyl, 2-benzimidazolyl, 2-quinolinyl, 3-quinolinyl, 1-isoquinolinyl, 3-isoquinolinyl, 1-isoindolyl, 3-isoindolyl, and acridinyl. Also included within the scope of the term "aromatic group", as it is used herein, is a group in which one or more carbocyclic aromatic rings and/or heteroaryl rings are fused to a cycloalkyl or non-aromatic heterocyclic ring. Examples include benzocyclopentane, benzocyclohexane, decalin, phthalimido, benzodiazepines, benzooxazepines, benzooxazines, phenothiazines, and groups represented by the following structural formulas:

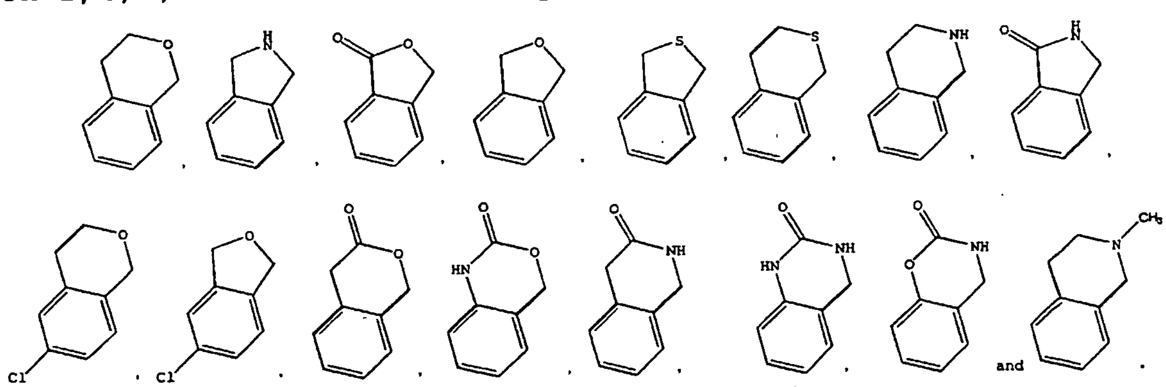
 ,  ,

 ,  ,

 ,  ,

or 

Non-aromatic heterocyclic rings are non-aromatic carbocyclic rings which include one or more heteroatoms such as nitrogen, oxygen or sulfur in the ring. The ring can be five, six, seven or eight-membered and/or fused to another ring, such as a cycloalkyl or aromatic ring. Examples include, for example, 1,3-dioxolan-2-yl,3-1H-benzimidazol-2-one, 3-1-alkyl-benzimidazol-2-one, 3-1-methyl-benzimidazol-2-one, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahyrothiophenyl, 3-tetrahyrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl , 4-thiazolidinyl, diazolonyl, N-substituted diazolonyl, 1-phthalimidyl, 1-3-alkyl-phthalimidyl, benzoxane, benzopyrolidine, benzopiperidine, benzoxolane, benzothiolane, benzothiane, tetrahydrofuran-2-one-3-yl, 2,5-dihydro-5-oxo-4H-1,2,4-thiadiazol-3-yl, 2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl,



"Heterocyclic ring", includes "heteroaryl group" and "non-aromatic heterocylic ring", and is defined as imidazole, benzimidazole, pyridine, pyrimidine, thiazole, benzothiazole, thienyl, benzothienyl.

Suitable substituents on an alkyl, aliphatic, aromatic, non-aromatic heterocyclic ring or benzyl group include, for example, an electron withdrawing group, an aliphatic group, substituted aliphatic group, azido, -OH, a halogen (-Br, -Cl, -I and -F), -O-(aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group), -CN, $-NO_2$, -COOH, $-NH_2$, -NH(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group), -N-(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group)$_2$, -COO(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group), $-CONH_2$, -CONH(aliphatic, substituted aliphatic group, benzyl, substituted benzyl, aromatic or substituted aromatic group), -CON(aliphatic, substituted aliphatic group, benzyl, substituted benzyl, aromatic or substituted aromatic group)$_2$, $-OSO_2NH_2$, $-OSO_2NH$(aliphatic, substituted aliphatic group, benzyl, substituted benzyl, aromatic or substituted aromatic group), $-OSO_2N$(aliphatic, substituted aliphatic group, benzyl, substituted benzyl, aromatic or substituted aromatic group)$_2$, $-SO_2NH_2$, $-SO_2NH$(aliphatic, substituted aliphatic group, benzyl, substituted benzyl, aromatic or substituted aromatic group), $-SO_2N$(aliphatic, substituted aliphatic group, benzyl, substituted benzyl, aromatic or substituted aromatic group)$_2$, -SH, $-SO_k$(aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group) (k is 0, 1 or 2), $-NH-C(=NH)-NH_2$, ureido, oxalo, amidino, $-C(=NR^{60})NR^{21}R^{22}$, $=NR^{60}$, $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$, -Q-H, -Q-(aliphatic group), -Q-(substituted aliphatic group), -Q-(aryl), -Q-(aromatic group), -Q-(substituted aromatic

group), -Q-$(CH_2)_p$-(substituted or unsubstituted aromatic group) (p is an integer from 1-5), -Q-(non-aromatic heterocyclic group) or -Q-$(CH_2)_p$-(non-aromatic heterocyclic group).

R^{20}, R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -NHC(O)-O-(aliphatic group), -NHC(O)-O-(aromatic group) or -NHC(O)-O-(non-aromatic heterocyclic group),or R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

R^{60} is a -H, -OH, $-NH_2$, an aromatic group or a substituted aromatic group.

t is an integer from zero to about three, and the methylene group, $-(CH_2)_t-$, can be substituted, as described herein for aliphatic groups, or unsubstituted.

u is zero or one.

Q is -O-, -S-, -S(O)-, $-S(O)_2-$, $-OS(O)_2-$, -C(O)-, -OC(O)-, -C(O)O-, -C(O)C(O)-O-, -O-C(O)C(O)-, -C(O)NH-, -NHC(O)-, -OC(O)NH-, -NHC(O)O-, -NH-C(O)-NH-, $-S(O)_2NH-$, $-NHS(O)_2-$, $-N(R^{23})-$, $-C(NR^{23})NHNH-$, $-NHNHC(NR^{23})-$, $-NR^{24}C(O)-$ or $-NR^{24}S(O)_2-$.

R^{23} is -H, an aliphatic group, a benzyl group, an aryl group or non-aromatic heterocyclic group.

R^{24} and R^{25} are independently -H, -OH, an aliphatic group, a substituted aliphatic group, a benzyl group, an aryl group, non-aromatic heterocyclic group, or R^{24} and R^{25} taken together with the nitrogen atom to which they are bonded can form a substituted or unsubstituted non-aromatic heterocyclic ring.

A substituted non-aromatic heterocyclic ring, benzyl group or aromatic group can also have an aromatic group, an aliphatic or substituted aliphatic group, as a substituent. When a non-aromatic ring (carbocyclic or heterocyclic) or an aromatic ring (carbocyclic aromatic or heteroaryl) is substituted with another ring, the two rings can be fused. A substituted aliphatic group can also have an oxo group, epoxy

group, non-aromatic heterocyclic ring, benzyl group, substituted benzyl group, aromatic group or substituted aromatic group as a substituent. A substituted non-aromatic heterocyclic ring can also have =O, =S, =NH or =N(aliphatic, aromatic or substituted aromatic group) as a substituent. A substituted aliphatic, substituted aromatic, substituted non-aromatic heterocyclic ring or substituted benzyl group can have more than one substituent, which can be the same or different.

Suitable electron withdrawing groups include, for example, alkylimines, alkylsulfonyl, carboxamido, carboxylic alkyl esters, -CH=NH, -CN, $-NO_2$ and halogens.

Acyl groups include substituted and unsubstituted aliphatic carbonyl, aromatic carbonyl, aliphatic sulfonyl and aromatic sulfonyl.

The compounds disclosed herein can be obtained as different sterioisomers (e.g., diastereomers and enantiomers). For example, when the antagonist of chemokine receptor function is represented by Structural Formula (I) and Z is represented by Structural Formula (IV), the carbon atom in Ring C which is bonded to Y may be in the R or S sterioconfiguration. It is pointed out that the invention includes all isomeric forms and racemic mixtures of the disclosed compounds and a method of treating a subject with both pure isomers and mixtures thereof, including racemic mixtures. It is understood that one sterioisomer may be more active than another. The desired isomer can be determined by screening for activity, employing the methods described herein.

In the structural formulas depicted herein, the single or double bond by which a chemical group or moiety is connected to the remainder of the molecule or compound is indicated by the following symbol:

 .

For example, the corresponding symbol in Structural Formula (V) or (VIII) indicates that the tricyclic ring system, which represents Z in Structural Formula (I), is connected to the alkylene group in Structural Formula (I) by a single covalent bond between the alkylene group and the ring carbon in Ring C which is bonded to W.

A "subject" is preferably a bird or mammal, such as a human, but can also be an animal in need of veterinary treatment, e.g., domestic animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, fowl, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

An "effective amount" of a compound is an amount which results in the inhibition of one or more processes mediated by the binding of a chemokine to a receptor in a subject with a disease associated with aberrant leukocyte recruitment and/or activation. Examples of such processes include leukocyte migration, integrin activation, transient increases in the concentration of intracellular free calcium $[Ca^{2+}]_i$ and granule release of proinflammatory mediators. Alternatively, an "effective amount" of a compound is a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in the prevention of or a decrease in the symptoms associated with a disease associated with aberrant leukocyte recruitment and/or activation.

The amount of compound administered to the individual will depend on the type and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type of disease. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. Typically, an effective amount of the compound can range from about 0.1 mg per day to about 100 mg per day for an adult. Preferably, the dosage ranges from about 1 mg per day to about 100 mg per day. An antagonist of chemokine receptor function can also

be administered in combination with one or more additional therapeutic agents, e.g. theophylline, β-adrenergic bronchodilators, corticosteroids, antihistamines, antiallergic agents, immunosuppressive agents (e.g., cyclosporin A, FK-506, prednisone, methylprednisolone) and the like.

The compound can be administered by any suitable route, including, for example, orally in capsules, suspensions or tablets or by parenteral administration. Parenteral administration can include, for example, systemic administration, such as by intramuscular, intravenous, subcutaneous, or intraperitoneal injection. The compound can also be administered orally (e.g., dietary), topically, transdermally, by inhalation (e.g., intrabronchial, intranasal, oral inhalation or intranasal drops), or rectally, depending on the disease or condition to be treated. Oral or parenteral administration are preferred modes of administration.

The compound can be administered to the individual in conjunction with an acceptable pharmaceutical or physiological carrier as part of a pharmaceutical composition for treatment of HIV infection, inflammatory disease, or the other diseases discussed above. Formulation of a compound to be administered will vary according to the route of administration selected (e.g., solution, emulsion, capsule). Suitable carriers may contain inert ingredients which do not interact with the compound. Standard pharmaceutical formulation techniques can be employed, such as those described in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. Suitable pharmaceutical carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Methods for encapsulating compositions (such as in a coating of hard gelatin or cyclodextran) are known in

the art (Baker, *et al.*, "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).

The activity of compounds of the present invention can be assessed using suitable assays, such as receptor binding assays and chemotaxis assays. For example, as described in the Exemplification Section, small molecule antagonists of RANTES and MIP-1α binding have been identified utilizing THP-1 cells which bind RANTES and chemotax in response to RANTES and MIP-1α as a model for leukocyte chemotaxis. Specifically, a high through-put receptor binding assay, which monitors ^{125}I-RANTES and ^{125}I-MIP-1α binding to THP-1 cell membranes, was used to identify small molecule antagonists which block binding of RANTES and MIP-1α. Compounds of the present invention can also be identified by virtue of their ability to inhibit the activation steps triggered by binding of a chemokine to its receptor, such as chemotaxis, integrin activation and granule mediator release. They can also be identified by virtue of their ability to block RANTES and MIP-1α mediated HL-60, T-cell, peripheral blood mononuclear cell, and eosinophil chemotactic response.

The compounds disclosed herein can be prepared accordingly to the schemes shown in Figures 1-5 and 7-8. The schemes are described in greater detail below.

Figure 1 is a schematic showing the preparation of the compounds represented by Structural Formulas (I) and (II), wherein Z is represented by Structural Formula (IV), wherein W is CN.

L^1, L^2 and L^3 in Figure 1 are suitable leaving groups such as halogen; p-toluene sulfonate, mesylate, alkoxy and phenoxy. The other symbols are as defined above.

The reduction reaction in Step 1 of Figure 1 is performed with a reducing agent such as or sodium borohydride or lithium aluminum hydride (LAH) in an inert solvent such as methanol or tetrahydrofuran (THF). The reaction is carried out at temperatures ranging from 0°C up to the reflux temperature and for 5 minutes to 72 h.

Compounds represented by formula II in Figure 1 can be prepared by procedures disclosed in JP 61/152673, U.S. Patent 5089496, WO 89/10369, WO 92/20681 and WO 93/02081, the entire teachings of which are incorporated herein by reference.

A chlorination reaction in step 2 of Figure 1 can be performed with reagents such as thionyl chloride. The reaction can be carried out in an inert solvent such as methylene chloride at 0°C up to the reflux temperature for 5 minutes to 72 h. The hydroxy group can be also converted to other leaving groups by methods familiar to those skilled in the art.

The cyanation reaction in step 3 of Figure 1 can be carried out using reagents such as copper cyanide, silver cyanide or sodium cyanide in an inert solvent such as benzene or toluene. Reaction temperatures range from 0°C up to the reflux temperature for 5 minutes to 72 h. Compounds represented by Formula V in Figure 1 can also be prepared by the procedures described in J. Med. Chem. 1994, 37, 804-810 and U.S. Patent 5672611, the entire teachings of which are incorporated herein by reference.

The alkylation reactions in steps 4 and 5 of Figure 1 can be carried out in a solvent such as acetone, methyl ethyl ketone, ethyl acetate, toluene, tetrahydrofuran (THF) or dimethylformamide (DMF) in the presence of a base such as potassium carbonate or sodium hydride and a catalyst such as an alkali metal iodide (when necessary). The reaction temperature can range from room temperature up to the reflux temperature and for 5 minutes to 72 h.

The product of the synthetic scheme shown in Figure 1 can be decyanated using a reducing agent such as lithium aluminum hydride (LAH) in an inert solvent such as ether or tetrahydrofuran (THF) at 0°C up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Figure 2 is a schematic showing the preparation of representative compounds of Structural Formula (I) and (II), wherein Z is represented by Structural Formulas (IV) and wherein

Ring A and/or Ring B in Z can be substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)-O-R^{20}$.

In Figure 2, the hydrolysis reaction may be carried out in a mixture of aqueous alkali metal hydroxide solution and a solvent such as methanol, ethanol, tetrahydrofuran (THF) or dioxane at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h. The acylation reaction can be carried out using dicyclohexylcarbodiimide (DCC) or (1-ethyl-3-(3- dimethylaminopropyl)carbodiimide (DEC) in a solvent such as tetrahydrofuran (THF), dimethylformamide (DMF) or methylene chloride in the presence of a base such as pyridine or triethylamine (when necessary) at temperatures of 0 to 100°C for 5 minutes to 72 h.

Compounds represented by Structural Formulas (I) and (II), wherein Z is represented by Structural Formulas (XVI), X is $-CO-N(R_c)-$ and R_c is $-(CH_2)_s-COOR^{30}$, $-(CH_2)_s-C(O)-NR^{31}R^{32}$ or $-(CH_2)_s-NHC(O)-O-R^{30}$, can be prepared by suitable modification of the scheme shown in Figure 1. One modification utilizes the starting material shown in Figure 1, wherein X is -CO-NH-. The amide is then alkylated with $L^3-(CH_2)_s-COOR^{30}$ using the alkylation procedures described above. L^3 is a suitable leaving group. The remainder of the synthesis is as described in Figures 1 and 2.

Figure 3 is a schematic showing the preparation of the compounds represented by Structural Formula (I) and (II), wherein Z is represented by Structural Formulas (VIII) and (XIII)-(XVI) and wherein V is W_a.

The reduction of the cyano group to an amine in Figure 3 can be carried out using metal hydrides or by catalytic reduction processes. Suitable reducing agents include lithium aluminum hydride (LAH), diisobutyl aluminum hydride (DIBAL-H), borane-methyl sulfide complex or sodium borohydride. The reduction can be carried out in an inert solvent such as ether, tetrahydrofuran (THF), methylene chloride or methanol at -78°C up to the reflux temperature for 5 minutes to 72 h. It is also possible to isolate the

corresponding imine intermediate, which can be converted to the amine using similar reduction processes.

Figure 4 is a schematic showing the preparation of compounds represented by Structural Formulas (I) and (II), wherein Z is represented by Structural Formula (IV), wherein W is H. The reduction of the double bond in step 1 of Figure 4 can be carried out using the catalytic reduction process. Suitable catalyst include palladium-carbon, platinum oxide or Ranney-nickel. The reduction can be carried out in an inert solvent such as methanol, ethanol or acetic acid at temperatures of 0 to 70°C under a hydrogen pressure of 1 to 100 atm for 5 minuets to 72 h. The alkylation reactions in step 2 of Figure 4 can be carried out using the same reactants and conditions as those in step 5 of Figure 1.

Figure 5 is a schematic showing the preparation of compounds represented by Structural Formulas (I) and (II), wherein Z is represented by Structural Formula (IV), wherein W is H. The alkylation reaction in step 1 of Figure 5 can be carried out using the same reactants and conditions as those in step 5 of Figure 1. The reduction of the double bond in step 2 of Figure 5 can be carried out using the same reactants and conditions as those in step 1 of Figure 4.

Figure 7 shows the preparation of compounds represented by Structural Formula (I), where in Z is represented by Structural Formulas (VI) and wherein Ring A and/or Ring B in Z is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, u is one. In Figure 7, the alkylation reaction may be carried out in a solvent such as acetone, methyl ethyl ketone, ethyl acetate, toluene, tetrahydrofuran (THF) or dimethylformamide (DMF) in the presence of a base such as potassium carbonate or sodium hydride and a catalyst such as an alkali metal iodide at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Figure 8 shows the preparation of compounds represented by Structural Formula (I), wherein Z is represented by Structural Formulas (VI) and wherein Ring A or Ring B in Z is substituted with $-(O)_u-(CH_2)_t-COOR^{20}$, u is zero. L4 is a

suitable leaving group such as halogen or trifluoromethylsulfonate. In Figure 8, a palladium coupling reaction such as Stille coupling, Suzuki coupling, Heck reaction, or carboxylation using carbon monoxide can be carried out using a palladium catalyst such as tetrakis(triphenylphosphine)palladium, bis(triphenylphosphine)palladium chloride, and palladium acetate in a solvent such as tetrahydrofuran (THF), 1,4-dioxane, toluene, dimethylformamide (DMF), or dimethylsufoxide (DMSO) in the presence of additive (when necessary) such as triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, triethylamine, sodium bicarbonate, tetraethylammonium chloride, or lithium chloride at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h. Figure 8B shows the preparation of N-benzyl-4-(4-chlorophenyl)-4-hydroxypiperidine.

Step 1

To a stirred solution of commercially available 4-(4-chlorophenyl)-4-hydroxypiperidine (10 g, 47 mmol., **1**) in anhydrous DMF (10 mL) was added benzyl bromide (5.6 mL, 47 mmol) and K_2CO_3 (7.4 g, 94 mmol.) and stirred at RT overnight. Excess solvent was removed under reduced pressure, brought up into CH_2Cl_2 (100 mL) washed with H_2O (2 X 50 mL). Organic layer separated, dried over Na_2SO_4 and charged on a silica gel flash column. Eluting off with 2% MeOH/CH_2Cl_2 10 g **2** (80% yield) was obtained as a viscous liquid. MS m/z: (M+ 303)

Step 2

N-benzyl-4-(4-chlorophenyl)-4-fluoropiperidine

To a cold (-78°C) solution of **2** (10 g, 33 mmol) in CH_2Cl_2 (20 mL) was slowly added DAST (diethylaminosulfur trifluoride, 5.3 mL, 39.8 mmol) under an inert atmosphere. The reaction was stirred at -78°C for an additional 45 min.

The reaction was quenched at −78°C by the slow addition of enough saturated aqueous sodium bicarbonate solution to afford a pH >8. This reaction resulted a quantitative conversion of the starting material to a 1:1 mixture of fluoropiperidine **3** and 4-(4-chlorophenyl)tetrahydropyridine **4**. The mixture of **3** and **4** (3.5 g, mixture, ~35% yield) was purified via silica gel flash chromatography, eluting with 2% $MeOH/CH_2Cl_2$. This mixture proved to be inseparable by silica gel flash chromatography. In order to separate out the desired product, the mixture of **3** and **4** were subjected to osmium tetroxide oxidation.

To a stirred solution of the mixture of **3** and **4** (1.8 g) in acetone/H_2O (5:1, 10 mL) was added a catalytic amount of OsO_4 in isopropanol (2.5 mol %, 1 mL) and *N*-methylmorpholine-*N*-oxide (0.69 g, 6.56 mmol). The reaction was stirred at RT overnight. The reaction was then evaporated to dryness, brought up into CH_2Cl_2 and washed with NaHSO3. This reaction resulted in the dihydroxylation of the undesired **4** to **5** and the clean separation of the desired fluoropiperidine **3** (1.0 g, 55% yield) from the byproduct by silica gel flash chromatography eluting with 2% $MeOH/CH_2Cl_2$. MS m/z: (M+306)

Step 3

4-(4-chlorophenyl)-4-fluoropiperidine

To a cold (0°C) solution of **3** (1.07 g, 3.5 mmol) in 1,2-dichloroethane was added 1,1-chloroethylchloroformate (0.45 mL, 4.2 mmol). The reaction was then heated to reflux for 2 hrs. Excess solvent was removed and the residue was brought up into 5 mL methanol. The mixture was refluxed for 2 hrs and excess methanol was removed under reduced pressure. Precipitation of the hydrochloride salt of **6** by the addition of CH_2Cl_2/hexane (1:1) followed by filtration resulted in the quantitative isolation of the desired crystalline product **6** (80%, 0.70 g). MS m/z: (M+215)

The product of this scheme can be used to prepare compounds of Structural Formula (I) wherein R^1 is -F.

Figure 8C shows the preparation of 4-azido-4-(4-chlorophenyl)piperidine.

To a cold (0°C) solution of **1** (3.0 g, 14 mmol) in anhydrous dioxane (15 mL) under an inert atmosphere was added NaN_3 (1.0 g, 15.4 mmol) followed by the slow dropwise addition of and BF_3●OEt (4.4 mL, 35 mmol). The reaction was stirred at 0°C for 3 hrs and was quenched at 0°C by the slow careful addition of saturated aqueous $NaHCO_3$ to basicity. The organic layer was separated and dried over Na_2SO_4. The reaction mixture was purified via silica gel flash chromatography eluting a 2 g 1:3 mixture of azidopiperidine **2** and olefin **3** with 2% $MeOH/CH_2Cl_2$. The mixture can be used directly to prepare compounds represented by Structural Formula (I) wherein R^1 is $-N_3$.

Figure 8D shows the preparation of *N*-benzyl-4-methylpiperidine.

Step 1

To a cold (-78°C) stirred solution of 1.4 M methyllithium in THF (39 mL, 54 mmol) under an inert atmosphere was added *N*-benzyl-4-oxopiperidine (**1**, 5.1 g, 27 mmol). The reaction was stirred at -78°C for 2hrs. The reaction was quenched by the slow addition of saturated aqueous NH_4Cl, the organic layer was separated and dried over Na_2SO_4. Pure methylpiperidine (**2**) was isolated via silica gel flash chromatography eluting with 5% $MeOH/CH_2Cl_2$. MS m/z: (M+206)

Step 2

N-benzyl-4-(4-chlorophenyl)-4-methylpiperidine:

To a flask containing chlorobenzene (10 mL, excess) and methylpiperidine (0.42 g, 2.06 mmol, **2**) was added aluminum trichloride (1.65 mL, 12.4 mmol). The reaction was heated to reflux for 24 hrs. Excess chlorobenzene was removed under

reduced pressure and pure **3** was obtained via silica gel flash chromatography eluting with % EtOAc/hexane. MS m/z: (M+ 300)

Step 3

4-(4-chlorophenyl)-4-methylpiperidine: Fig. 8D

To a cold (0°C) solution of *N*-benzyl-4-(4-chlorophenyl)-4-methylpiperidine (**3**) (0.41 g, 1.4 mmol) in CH_2Cl_2 was 1.1 equivalent of 1-chloroethylchloroformate. The reaction was then heated to reflux for 2 hrs. Excess solvent was removed and the residue was brought up into methanol. The mixture was refluxed for 2 hrs and excess methanol was removed under reduced pressure. Precipitation of the hydrochloride salt **4** by the addition of CH_2Cl_2 followed by filtration resulted in the quantitative isolation of the desired crystalline product **4** (100%, 0.34 g). MS m/z: (M+ 210)

The product of this scheme can be used to prepare compounds of Structural Formula (I) wherein R^1 is $-CH_3$.

Figures 9A shows the preparation of compounds represent by Structural Formula (I) wherein R^1 is an amine. The azido functionality can be reduced with a variety of reducing agents such as triphenylphosphine, lithium aluminum hydride, sodium borohydride, in a solvent such as tetrahydrofuran or diethyl ether in reaction temperature ranges from 0°C to reflux with a reaction time of between 5 minutes and 72 hours.

Figure 9B shows the preparation of compounds represent by Structural Formula (I) wherein R^1 is -CH2NH2. To a cold (0°C) stirred solution of cyano containing molecule (0,50 g, 0.14 mmol) in a solvent such as diethyl ether or THF (5 mL) can be added a reducing agent such as lithium aluminum hydride (8 mg, 0.21 mmol). The reaction can then be stirred at 0°C to reflux from 5 minutes to 72 hurs. The reaction can then be quenched by the careful addition of H_2O (o.21 mL), 15% aqueous KOH (0.21 mL). The organic payer can then be separated and dried over Na_2SO_4.

Pure amino compound can be obtained via silica gel flash chromatography.

Figure 9C shows the preparation of 2-(4-chlorophenyl)-1-(*N*-methyl)ethylamine.

Step 1

To a solution of $AlCl_3$ (1.96 g, 14.7 mmol) in anhydrous CH_2Cl_2 (50 mL), Borane-*tert*-butyl amine complex (2.57 g, 29.6 mmol) was added at 0°C under argon protection, stirred for 10 minutes and clear solution was formed. 4-Chlorophenacyl bromide (**1**, 1.11 g, 4.91 mmol) in CH_2Cl_2 (5 mL) was added to the resulted mixture at 0°C. The reaction was stirred for 1.5 hours and then quenched by the addition of 0.1 N HCl (25 mL). The mixture was extracted with EtOAc (80 mL x 3), dried over MgSO4 and concentrated in vacuo. Chromatographic purification on silica gel (Hexane/EtOAc = 9:1) provided 0.85 g (84%) of 2-(4-chlorophenyl)-1-bromoethylene (**2**). MS m/z: (M+ 219).

Step 2

A mixture of 2-(4-chlorophenyl)-1-bromoethylene (**2**, 1.02 g, 4.62 mmol), EtOH (3 mL) and H_2NMe in H_2O (6 mL, 40% w/w) was heated at 135 0°C over night. The mixture was cooled down to room temperature. The mixture was extracted with Et_2O (5mL x 2), dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification on silica gel (CH_2Cl_2/MeOH/NH_4OH = 9/1/0.1) provided 0.61 g 2-(4-chlorophenyl)-1-(*N*-methyl)ethylamine (**3**, 79%).

MS m/z: (M+ 170).

Figure 9D shows the preparation of 3-(4-chlorophenyl)-3-hydroxyl-3-methyl-1-*N*-methylaminopropane

Step 1

To 3,4'-Dichloropropylphenone (**1**, 1.10 g, 5.40 mmol) in anhydrous THF at 0°C under the protection of argon, was added MeMgBr (2.50 mL, 7.35 mmol) dropwise at 0°C. The reaction was stirred at room temperature for an additional hour. The

reaction was quenched by adding saturated aqueous NH_4Cl. The reaction was then extracted with Et_2O (60 mL x 2), dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification on silica gel (Hexane/EtOAc = 10/1) provided 1.0 g (85%) of 3-(4-chlorophenyl)-3-hydroxy-3-methyl-1-bromoropane (**2**). MS m/z: (M+ 219).

Step 2

A mixture of 3,3,3-(4-Chlorophenyl)-hydroxylmethyl-1-bromoropane (**2**, 1.04 g, 4.74 mmol), EtOH (5 mL) and H_2NMe in H_2O (10 mL, 40% w/w) was heated at 135 0°C for 3 hours. The mixture was cooled down to room temperature. The mixture was extracted with Et_2O (5mL x 2), dried over $MgSO_4$ and concentrated in vauco. Chromatographic purification on silica gel (CH_2Cl_2/MeOH/NH_2OH = 9/1/0.1) provided 1.01 g 3-(4-chlorophenyl)-3-hydroxyl-3-methyl-1-*N*-methylaminopropane (**3**, 99%). MS m/z: (M+ 214).

Figure 9E shows the preparation of 3-(4-chlorophenyl)-1-*N*-methylaminopropane.

A mixture of 3-(4-chlorophenyl)-1-bromoropane (**1**, 0.70 g, 3.73 mmol), EtOH (3 mL) and H_2NMe in H_2O (6 mL, 40% w/w) was heated at 135 0°C overnight. The mixture was then cooled down to room temperature. The mixture was extracted with Et_2O (5 mL x 2), dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification on silica gel (CH_2Cl_2/MeOH/NH_4OH = 9/1/0.1) provided 0.5 g (76%) of 3-(4-chlorophenyl)-1-*N*-methylaminopropane (**2**). MS m/z: (M+ 189).

Figure 10A shows the preparation of 3-(4-chlorophenyl)-3-hydroxyl-3-methyl-1-*N*-methylaminopropane.

Step 1

To 3,4'-Dichloropropylphenone (**1**, 1.10 g, 5.40 mmol) in anhydrous THF at 0°C under the protection of argon, was added MeMgBr (2.50 mL, 7.35 mmol) dropwise at 0°C. The reaction was stirred at room temperature for an additional hour. The reaction was quenched by adding saturated aqueous NH_4Cl. The

reaction was then extracted with Et_2O (60 mL x 2), dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification on silica gel (Hexane/EtOAc = 10/1) provided 1.0 g (85%) of 3-(4-chlorophenyl)-3-hydroxy-3-methyl-1-bromoropane (**2**). MS m/z: (M+ 219).

Step 2

A mixture of 3,3,3-(4-Chlorophenyl)-hydroxylmethyl-1-bromoropane (**2**, 1.04 g, 4.74 mmol), EtOH (5 mL) and H_2NMe in H_2O (10 mL, 40% w/w) was heated at 135 0°C for 3 hours. The mixture was cooled down to room temperature. The mixture was extracted with Et_2O (5mL x 2), dried over $MgSO_4$ and concentrated in vauco. Chromatographic purification on silica gel (CH_2Cl_2/MeOH/NH_2OH = 9/1/0.1) provided 1.01 g 3-(4-chlorophenyl)-3-hydroxyl-3-methyl-1-*N*-methylaminopropane (**3**, 99%). MS m/z: (M+ 214).

Figure 10b shows the preparation of 1-(4-chlorobenzoyl)-1,2-ethylenediamine

Step 1

tert-Butyl *N*-(2-aminoethyl) carbamate (**1**, 0.50 g g, 3.12 mmol) was added to the mixture of 4-chlorobenzoic acid chloride (0.547 g, 3.12 mmol) and Et_3N (1.74 mL, 12.5 mmol) in CH_2Cl_2 (20 mL) under the protection of argon. Stirring at room temperature for 2 hours. The reaction mixture was diluted with H_2O (25 mL), extracted with CH_2Cl_2 (50 mL x 2), dried over $MgSO_4$ and concentrated in vacuo. Chromatographic purification on silica gel (CH_2Cl_2/MeOH = 95/5) to provide 0.86 g (**2**, 93%) of the desired product *tert*-Butyl 3-(4-chlorobenzoyl)-1-(2-aminoethyl) carbamate. MS m/z: (M+ 299).

Step 2

Trifluoroacetic acid (7.5 mL) was added to the solution of *tert*-Butyl 3-(4-chlorobenzoyl)-1-(2-aminoethyl)carbamate (**2**, 0.86 g, 2.89 mmol) in CH_2Cl_2 (35 mL) at 0°C. Stirring at room temperature for 30 minutes. Concentration in vacuo provided

0.88 g (95%) of the desired product 1-(4-chlorobenzoyl)-1,2-ethylenediamine (**3**). MS m/z: (M+ 199).

Compounds prepared according to the schemes presented in Figures 9C-9E, 10A and 10B can be used to prepare compounds represented by Structural Formula (XXVI).

Figure 10C shows three procedures for the preparation of compounds represented by Structural Formulas (I),(VII), (VIII) and (IX), wherein Z is represented by Structural Formula (III) and wherein Ring A or Ring B in Z is substituted with R^{40}. In Figure 10C, R^{40} is represented by $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$, u is one, t is zero.

In Figure 10C a compound containing a phenol can be reacted with a carbonate equivalent, such as a carbamoyl chloride (method A), an isocyanate (method B) or an acylimidazole (method C), in the presence of a base such as sodium hydroxide, potassium carbonate or sodium carbonate in a solvent such as dimethylformamide or tetrahydrofuran, at a temperature from 0°C to reflux temperature for a period of about 5 minutes to about 72 hours.

Figure 12 shows the preparation of compounds represented by Compound (XV-b). In Step 1 of Figure 12, a Grignard reaction can be carried out in a solvent such as ether, or tetrahydrofuran (THF) at 0°C up to the reflux temperature for the solvent used for 5 minuets to 72 h. Compound XIII is available commercially.

In Step 2 of Figure 1, bromination can be carried out with brominate agents such as hydrobromic acid, bromotrimethylsilane or boron tribromide-methyl sulfide complex in a solvent such as acetic acid, dichloromethane or dichloroethane at room temperature up to the reflux temperature for the solvent used for 5 minutes to 72 h.

Figure 13 shows the preparation of compounds of formula (XV-c). The Friedel-Crafts acylation can be carried out using an acid chloride in the presence of a Lewis acid, such as aluminum trichloride or titanium tetrachloride, in a solvent

such as dichloromethane, dichloroethane, nitrobenzene or carbon disulfide. The acylation reaction can be run at a temperature of about room temperature up to the reflux temperature of the chosen solvent, and for a period of about 5 minutes to about 72 hours.

Figure 14 shows the preparation of compounds of formula (XV-e). In Step 1 of Figure 13, a chlorosulfonylation can be carried out using chlorosulfonic acid in a solvent, such as dichloromethane, or in the absence of a solvent at a temperature of about 0°C to about 60°C for a period of about 5 minutes to about 72 hours. In Step 2 of Figure 12, a coupling reaction can be carried out using an amine in the presence of a base, such as triethylamine, in a solvent such as dichloromethane, acetone, ethanol, THF or DMF. The reaction can be carried out at a temperature of about room temperature up to the reflux temperature of the selected solvent, and for a period of about 5 minutes to about 72 hours.

Although Figures 1-5 and 6-7 and 12-14 show the preparation of compounds in which Rings A and B are phenyl rings, analogous compounds with heteroaryl groups for Rings A and B can be prepared by using the starting materials with heteroaryl groups in the corresponding positions, which can be prepared according to methods disclosed in JP 61/152673, U.S. Patent 5089496, WO 89/10369, WO 92/20681 and WO 93/02081.

The invention is illustrated by the following examples which are not intended to be limiting in any way.

EXEMPLIFICATION

Example 1 - Preparation of 4-(4-Chlorophenyl)1-[3-(5-cyano-5H-dibenzo[a,d]cycloheptene-5-yl)propyl]piperidin-4-ol

To a solution of 5H-dibenzo[a,d]cycloheptene-5-carbonitrile (described in J. Med Chem. 1994, 37, 804-810)(500mg) in DMF (10ml) were added 60% sodium hydride (110mg) and 1-bromo-3- chloropropane (0.30ml) and the mixture was stirred at room temperature for 1 hours. Water and ethyl

acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure to give 5-(3-chloropropyl-5H-dibenzo[a,d]cycloheptene- 5-carbonitrile. Without purification, to a solution obtained chloride in DMF (10ml) were added 4-(4-chlorophenyl)-4-hydroxypiperidine (650mg), potassium carbonate (950mg), and potassium iodide (50mg) and the mixture was stirred at 70°C for 24 hours. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:1) to give the titled compound (700mg). ^{1}H-NMR ($CDCl_3$) d: 1.22-1.34(2H,m), 1.60-1.80(3H,m), 1.93-1.99(2H,m), 2.16-2.28(6H,m), 2.56-2.60(2H,m), 6.98(2H,s), 7.25-7.47(10H,m), 8.00-8.03(2H,m). MS m/z: 469(M+1)

Example 2 - Preparation of 4-(4-Chlorophenyl)-1-[3-(5-cyano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-yl)propyl]piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) d: 1.43-1.49(2H,m), 1.61-1.66(2H,m), 1.93-2.02(3H,m), 2.24-2.32(4H,m), 2.48-2.62(4H,m), 2.96-3.06(2H,m), 3.35-3.45(2H,m), 7.11-7.41(10H,m), 7.93-7.97(2H,m). MS m/z: 471(M+1)

Example 3 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano-6,11-dihydrodibenz[b,e]oxepin-11-yl)propyl]piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 6,11-dihydrodibenz[b,e]oxepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.37-1.68(5H,m),

1.99-2.09(2H,m), 2.24-2.50(5H,m), 2.65-2.69(2H,m), 2.78-2.85(1H,m), 5.03(1H,d), 5.45(1H,d), 7.02-7.43(10H,m), 7.82-7.86(1H,m), 7.95-8.00(1H,m). MS m/z: 473(M+1)

Example 4 - Preparation of 1-[3-(11-Cyano-6,11-dihydrodibenz[b,e]oxepin-11-yl)propyl]-4-(4-fluorophenyl)piperidin-4-ol

Following the procedure of example 3, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-fluorophenyl)- 4-hydroxypiperidine, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.40-1.68(4H,m), 1.88-2.08(3H,m), 2.29-2.50(5H,m), 2.63-2.67(2H,m), 2.77-2.84(1H,m), 5.03(1H,d), 5.44(1H,d), 6.95-7.46(10H,m), 7.81-7.85(1H,m), 7.94-7.99(1H,m). MS m/z: 457(M+1)

Example 5 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano-6,11-dihydro-2-fluorodibenz[b,e]oxepin-11-yl)propyl]piperidin- 4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 6,11-dihydro-2-fluorodibenz[b,e]oxepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.37-1.69(5H,m), 1.98-2.09(2H,m), 2.25-2.48(5H,m), 2.65-2.70(2H,m), 2.78-2.87(1H,m), 5.01(1H,d), 5.42(1H,d), 6.99-7.11(3H,m), 7.25-7.43(6H,m), 7.54-7.59(1H,m), 7.92-7.95(1H,m). MS m/z: 491(M+1)

Example 6 - Preparation of 1-[3-(2-Bromo-11-cyano-6,11-dihydrodibenz[b,e]oxepin-11-yl)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 2-bromo-6,11-dihydrodibenz[b,e]oxepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.37-1.69(5H,m), 1.97-2.09(2H,m), 2.24-2.48(5H,m),

2.66-2.85(3H,m), 5.00(1H,d), 5.43(1H,d), 6.97-7.02(2H,m), 7.24-7.46(7H,m), 7.91-7.95(2H,m).
MS m/z: 551, 553(M+1)

Example 7 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano-6,11-dihydro-2-methyldibenz[b,e]oxepin-11-yl)propyl]piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 6,11-dihydro-2-methyldibenz[b,e]oxepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.40-1.70(5H,m), 1.98-2.09(2H,m), 2.25-2.52(8H,m), 2.68-2.73(2H,m), 2.81-2.90(1H,m), 5.00(1H,d), 5.44(1H,d), 6.98-7.43(9H,m), 7.63(1H,d), 7.94-7.98(1H,m). MS m/z: 487(M+1)

Example 8 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano-3,4-dichloro-6,11-dihydro-dibenz[b,e]oxepin-11-yl)propyl]piperidin- 4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 3,4-dichloro-6,11-dihydrodibenz[b,e]oxepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.40-1.71(5H,m), 2.00-2.10(2H,m), 2.28-2.50(5H,m), 2.65-2.85(3H,m), 5.04(1H,d), 5.46(1H,d), 6.99-7.03(1H,m), 7.26-7.44(7H,m), 7.91-7.95(2H,m).
MS m/z: 541(M+1)

Example 9 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11- cyano-6,11-dihydro-2,3-methylenedioxydibenz[b,e]oxepin-11-yl)propyl]piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 6,11-dihydro-2,3-methylenedioxydibenz[b,e]oxepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.60-1.90(5H,m),

2.30-2.50(2H,m), 2.80-3.30(8H,m), 5.05(1H,d), 5.45(1H,d), 6.02(2H,brd), 6.68(1H,s), 6.97-7.01(1H,m), 7.26-7.43(7H,m), 7.83-7.87(2H,m). MS m/z: 517(M+1)

Example 10 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl] piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 6,11-dihydrodibenzo[b,e]thiepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.63-1.76(5H,m), 2.03-2.16(2H,m), 2.37-2.52(4H,m), 2.72-2.85(3H,m), 3.03-3.10(1H,m), 4.10(1H,d), 4.54(1H,d), 7.13-7.44(10H,m), 7.81-7.87(2H,m). MS m/z: 489(M+1)

Example 11 - Preparation of 1-[3-(11-Cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]-4-phenylpiperidin-4-ol

Following the procedure of example 10, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-hydroxy-4-phenylpiperidine, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.63-1.77(5H,m), 2.02-2.16(2H,m), 2.37-2.52(4H,m), 2.72-2.85(3H,m), 3.03-3.10(1H,m), 4.10(1H,d), 4.55(1H,d), 7.13-7.52(10H,m), 7.81-7.88(2H,m). MS m/z: 455(M+1)

Example 12 - Preparation of 4-(4-Bromophenyl)-1-[3-(11-cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol

Following the procedure of example 10, but replacing 4-(4-chlorophenyl)-4-hydroxypiperidine with 4-(4-bromophenyl)-4- hydroxypiperidine, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.64-1.82(5H,m), 2.02-2.12(2H,m), 2.32-2.48(4H,m), 2.69-2.85(3H,m), 2.99-3.09(1H,m), 4.07(1H,d), 4.50(1H,d), 7.11-7.46(10H,m), 7.79-7.86(2H,m). MS m/z: 533, 535(M+1)

Example 13 - Preparation of 1-[3-(2-Bromo-11-cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]-4-(4-chlorophenyl)piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 2-bromo-6,11-dihydrodibenzo[b,e]thiepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.63-1.78(5H,m), 2.03-2.14(2H,m), 2.35-2.52(4H,m), 2.72-2.80(3H,m), 3.00-3.10(1H,m), 4.15(1H,brd), 4.50(1H,d), 7.07-7.45(10H,m), 7.73-7.81(1H,m), 7.95(1H,d). MS m/z: 567, 569(M+1)

Example 14, 15 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano-6,11-dihydro-5-oxodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 6,11-dihydro-5-oxodibenzo[b,e]thiepin-11-carbonitrile, the titled compound was prepared. The diastereomers were separated by silica gel chromatography. isomer 1 ^{1}H-NMR ($CDCl_3$) δ: 1.20-1.35(1H,m), 1.63-1.69(4H,m), 2.04-2.84(10H,m), 4.21(1H,d), 4.31(1H,d), 7.18-7.65(9H,m), 8.03-8.13(3H,m). MS m/z: 505(M+1) isomer 2 ^{1}H-NMR ($CDCl_3$) d: 1.25-1.38(1H,m), 1.65-2.15(6H,m), 2.28-2.82(8H,m), 4.65(1H,d), 4.82(1H,d), 7.27-7.56(9H,m), 7.92-8.00(3H,m). MS m/z: 505(M+1)

Example 16 - Preparation of 4-(4-Chlorophenyl)-1-[3-(11-cyano- 6,11-dihydro-5,5-dioxodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol

Following the procedure of example 1, but replacing 5H-dibenzo[a,d]cycloheptene-5-carbonitrile with 6,11-dihydro-5,5-dioxodibenzo[b,e]thiepin-11-carbonitrile, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.40-2.72(14H,m), 3.08-3.22(1H,m), 4.58(1H,d), 5.58(1H,d), 7.29-7.58(9H,m), 7.99-8.13(3H,m). MS m/z: 521(M+1)

Example 17 - Preparation of 4-(4-Chlorophenyl)-1-[3-(6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol

To a solution of4-(4-chlorophenyl)-1-[3-(11-cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol (430mg) in THF (10ml) was added 1M lithium aluminum hydride THF solution (1.5ml) and the mixture was heated to reflux for 3 hours. The reaction mixture was cooled with ice, water (0.06ml), then 15% aqueous sodium hydroxide (0.06ml), then water (0.18ml) were added carefully. The granular salt was filtered off and the filtrate was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:1) to give the titled compound (280mg).

^{1}H-NMR ($CDCl_3$) δ: 1.55-1.80(4H,m), 2.03-2.16(2H,m), 2.25-2.52(6H,m), 2.72-2.80(2H,m), 3.90(1H,brs), 4.48(1H,brt), 4.68(1H,brs), 6.96-7.45(12H,m). MS m/z: 464(M+1)

Example 18 - Preparation of 4-(4-Chlorophenyl)-1-[3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-yl)propyl]piperidin-4-ol

Following the procedure of example 17, but replacing 4-(4-chlorophenyl)-1-[3-(11-cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol with 4-(4-chlorophenyl)-1-[3-(5-cyano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-yl)propyl]piperidin-4-ol, the titled compound was prepared. ^{1}H-NMR ($CDCl_3$) δ: 1.40-1.58(2H,m), 1.62-1.71(2H,m), 1.98-2.20(4H,m), 2.30-2.42(4H,m), 2.67-2.78(2H,m), 2.95-3.08(2H,m), 3.30-3.44(2H,m), 4.01(1H,t), 7.10-7.46(12H,m). MS m/z: 446(M+1)

Example 19 - Preparation of 4-(4-Chlorophenyl)-1-[3-(6,11-dihydrodibenz[b,e]oxepin-11-yl)propyl]piperidin-4-ol

Following the procedure of example 17, but replacing 4-(4-chlorophenyl)-1-[3-(11-cyano-6,11-

dihydrodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol with 4-(4-chlorophenyl)-1-[3-(11-cyano-6,11-dihydrodibenz[b,e]oxepin- 11-yl)propyl]piperidin-4-ol, the titled compound was prepared.

^{1}H-NMR ($CDCl_3$) δ: 1.36-1.49(2H,m), 1.58-1.67(2H,m), 1.95-2.33(8H,m), 2.63-2.68(2H,m), 3.74(1H,t), 4.95(1H,d), 5.48(1H,d), 6.95-7.39(12H,m). MS m/z: 448(M+1)

Example 20 - Preparation of 4-(4-Chlorophenyl)-1-[3-(6,11-dihydro-11-iminomethyldibenzo[b,e]thiepin-11-yl)propyl]-piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(11-cyano-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol (1.92g) in dichloromethane (30ml) at -78°C was added 1M diisobutyl aluminum hydride dichloromethane solution (10ml). The reaction mixture was warmed to room temperature, and stirred for 30 minutes. Water and dichloromethane were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate to give the titled compound (1.16g).

^{1}H-NMR ($CDCl_3$) δ: 1.65-1.80(5H,m), 2.02-2.18(2H,m), 2.45-2.60(6H,m), 2.78-2.86(2H,m), 3.82(1H,d), 4.25(1H,d), 7.05-7.45(12H,m), 8.28(1H,brs). MS m/z: 491(M+1)

Example 21 - Preparation of 1-[3-(11-aminomethyl-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl]-4-(4-chlorophenyl)piperidin-4-ol

To a solution of 4-(4-chlorophenyl)-1-[3-(6,11-dihydro-11-iminodibenzo[b,e]thiepin-11-yl)propyl]piperidin-4-ol (600mg) in methanol (15ml) was sodium borohydride (220mg), and the mixture was stirred at room temperature for 10 hours. The solvent was distilled off under reduced pressure. Water and ethyl acetate were added to the reaction mixture, the organic

layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced to give the titled compound (600mg). MS m/z:493(M+1)

Example 22 - Preparation of Phenyl N-[11-[3-(4-(4-chlorophenyl)-4-hydroxypiperidino)propyl]-6,11-dihydrodibenzo[b,e]thiepin-11-yl)methyl carbamate

To a solution of 4-(4-chlorophenyl)-1-[3-(11-aminomethyl-6,11-dihydrodibenzo[b,e]thiepin-11-yl)propyl] piperidin-4-ol (610mg) in THF (20ml) was triethylamine (0.2ml) and phenyl chlorocarbonate (0.16ml) at 0°C, and the mixture was stirred for 1 hours. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate to give the titled compound (400mg).

^{1}H-NMR ($CDCl_3$) δ: 1.40-2.90(15H,m), 4.05-4.12(2H,m), 4.38(1H,d), 4.50-4.60(1H,m), 5.98(1H,brs), 6.96-7.54(17H,m).

MS m/z: 613(M+1)

Example 23 - Preparation of 1-[11-[3-(4-(4-chlorophenyl)-4-hydroxypiperidino)propyl]-6,11-dihydrodibenzo[b,e]thiepin-11-yl]methyl-8-(3-hydroxypropyl)urea

To a solution phenyl N-[2-[3-[4-(4-chlorophenyl)-4-hydroxypiperidino]propyl]-2-(6,11-dihydrodibenzo[b,e]thiepin-11-yl)ethyl] carbamate (300mg) in DMF (10ml) were added 3-amino-1-propanol (70mg), potassium carbonate (130mg) and the mixture was stirred at room temperature for 16 hours. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (9:1) to give the titled compound (200mg).

^{1}H-NMR ($CDCl_3$) δ: 1.40-1.70(6H,m), 2.01-2.08(2H,m), 2.30-2.63(8H,m), 3.12 (2H,q), 3.42(2H,t), 4.00-4.12(2H,m), 4.22-4.28(2H,m), 4.82(1H,brt), 4.99(1H,brs), 6.98-7.45(12H,m).MS m/z: 594(M+1)

Example 24 - Preparation of 4-(4-Chlorophenyl)-1-[3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-yl)-3-propioyl]piperidin-4-ol

To a solution 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-carbonitrile (500mg) in THF (5ml) was added 1.6M n-butyl lithium hexane solution (1.8ml) at 0°C. The mixture was warmed to room temperature, and stirred for 20 minutes. To the reaction mixture cooled to 0°C was added ethyl 3-(4-(4-chlorophenyl)-4- hydroxypiperidine-1-yl)propionate (310mg) dropwise as THF solution (2ml), and the mixture was warmed to room temperature, and stirred for 30 minutes. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:1) to give the titled compound (380mg).

^{1}H-NMR ($CDCl_3$) δ: 1.57-1.62(2H,m), 1.91-2.01(3H,m), 2.27-2.84(10H,m), 3.30-3.44(2H,m), 4.65(1H,s), 7.10-7.38(12H,m).

MS m/z: 460(M+1)

Examples 28 - 59 can be prepared by methods set forth in the schemes in Figure 1-5 and the procedures described above.

Example 60 - Membrane Preparations for Chemokine Binding and Binding Assays

Membranes were prepared from THP-1 cells (ATCC #TIB202). Cells were harvested by centrifugation, washed twice with PBS (phosphate-buffered saline), and the cell pellets were frozen at -70 to -85°C. The frozen pellet was thawed in ice-cold

lysis buffer consisting of 5 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethane-sulfonic acid) pH 7.5, 2 mM EDTA (ethylenediaminetetraacetic acid), 5 μg/ml each aprotinin, leupeptin, and chymostatin (protease inhibitors), and 100 μg/ml PMSF (phenyl methane sulfonyl fluoride - also a protease inhibitor), at a concentration of 1 to 5 x 10^7 cells/ml. This procedure results in cell lysis. The suspension was mixed well to resuspend all of the frozen cell pellet. Nuclei and cell debris were removed by centrifugation of 400 x g for 10 minutes at 4°C. The supernatant was transferred to a fresh tube and the membrane fragments were collected by centrifugation at 25,000 x g for 30 minutes at 4°C. The supernatant was aspirated and the pellet was resuspended in freezing buffer consisting of 10 mM HEPES pH 7.5, 300 mM sucrose, 1μg/ml each aprotinin, leupeptin, and chymostatin, and 10 μg/ml PMSF (approximately 0.1 ml per each 10^8 cells). All clumps were resolved using a minihomogenizer, and the total protein concentration was determined using a protein assay kit (Bio-Rad, Hercules, CA, cat #500-0002). The membrane solution was then aliquoted and frozen at -70 to -85°C until needed. Binding Assays utilized the membranes described above. Membrane protein (2 to 20 μg total membrane protein) was incubated with 0.1 to 0.2 nM ^{125}I-labeled RANTES or MIP-1α with or without unlabeled competitor (RANTES or MIP-1α) or various concentrations of compounds. The binding reactions were performed in 60 to 100 μl of a binding buffer consisting of 10 mM HEPES pH 7.2, 1 mM $CaCl_2$, 5 mM $MgCl_2$, and 0.5% BSA (bovine serum albumin), for 60 min at room temperature. The binding reactions were terminated by harvesting the membranes by rapid filtration through glass fiber filters (GF/B or GF/C, Packard) which were presoaked in 0.3% polyethyleneimine. The filters were rinsed with approximately 600 μl of binding buffer containing 0.5 M NaCl,

dried, and the amount of bound radioactivity was determined by scintillation counting in a Topcount beta-plate counter.

The activities of test compounds are reported in the Table below as IC_{50} values or the inhibitor concentration required for 50% inhibition of specific binding in receptor binding assays using ^{125}I-RANTES or ^{125}MIP-1α as ligand and THP-1 cell membranes. Specific binding is defined as the total binding minus the non-specific binding; non-specific binding is the amount of cpm still detected in the presence of excess unlabeled RANTES or ^{125}MIP-1α.

Table

BIOLOGICAL DATA

Example	IC_{50} (μM)
1	<1
2	<1
3	<1
4	<1
5	<1
6	<1
7	<1
10	<1
11	<100
12	<1
13	<1
14	<1
15	<1
16	<1
17	<1
18	<1
19	<1
22	<1
23	<10
24	<1
25	<1
26	<1
27	<1

Examples 61 can be prepared by methods set forth in the schemes in Figure 1-5 and the procedures described above.

Example 62 - 4-(4-Chlorophenyl)-1-[3-(5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-propyl]piperidin-4-ol

Step 1

To a solution of 5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-one (5.0g) in THF (50ml) was added 1.1M cyclopropylmagnesium bromide THF solution (25ml) at 0°C. The reaction mixture was warmed to room temperature, and stirred for 30 minutes. Aqueous ammonium chloride and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was filtered and washed with ethyl acetate-hexane (1: 2) to give 5-cyclopropyl-5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepin-5-ol (5.0g).

Step 2

To a solution of the product of step 1 (4.3g) in acetic acid (30ml) was added 48% aqueous HBr (25ml) at 10°C. The reaction mixture was warmed to room temperature, and stirred for 12 hours. Water and ethyl acetate were added to the reaction mixture and neutralized with dilute NaOH solution. The organic layer was separated and washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane (1:4) to give 5-(3-bromopropylidene)-5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepine (5.6g).

^{1}H-NMR ($CDCl_3$) δ: 2.74(2H,q), 3.46(2H,t), 3.78(3H,s), 5.25(2H,brs), 6.07(1H,t), 6.72-6.82(3H,m), 7.21-7.42(5H,m), 7.56(1H,dd), 8.45(1H,dd).

Step 3

To a solution of the product of step 2 (160mg) in ethanol (3ml) and acetic acid (1ml) were added 10% Pd-C (79mg) was stirred under hydrogen (under a balloon) at room temperature for 24 hour. The mixture was filtered through the celite and distilled off under reduced pressure. The residue was purified by preparative thin layer chromatography eluting with ethyl acetate-hexane (1:2) to give 5-(3-bromopropyl)-5,11-dihydro-7-methoxypyrido[2,3-c][1]benzoxepine (48mg).

^{1}H-NMR ($CDCl_3$) δ: 1.80-2.45(4H,m), 3.33-3.39(2H,m), 3.59(1h,dd), 3.77(3H,s), 4.98(1H,d), 5.44(1H,d), 6.70-6.79(2H,m), 7.08-7.14(5H,m), 7.52(1H,dd), 8.41(1H,dd).

Step 4

To a solution the product of step 3 (45mg) in DMF (1ml) were added 4-(4-chlorophenyl)-4-hydroxypiperidine (54mg) and potassium carbonate (19mg) and the mixture was stirred at 50°C for 1 hour. Water and ethyl acetate were added to the reaction mixture, the organic layer was separated and washed with saturated aqueous sodium chloride, and dried with magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate-methanol (10:1) to give the titled compound (19mg).

^{1}H-NMR ($CDCl_3$) δ: 1.50(1H,brs), 1.67-1.72(2H,m), 2.00-2.47(10H,m), 2.76-2.81(2H,m), 3.59(1H,dd), 3.77(3H,s), 4.97(1H,d), 5.43(1H,d), 6.72-6.78(2H,m), 7.06-7.13(2H,m), 7.26-7.44(4H,m), 7.52(1H,dd), 8.37(1H,dd).

MS m/z: 479(M+1)

Examples 63 - 417 can be prepared by methods set forth in the schemes in Figure 1-5, 6-7, 8A-8C, 9A-9E, 10A-10E and 12-14, and the procedures described above.

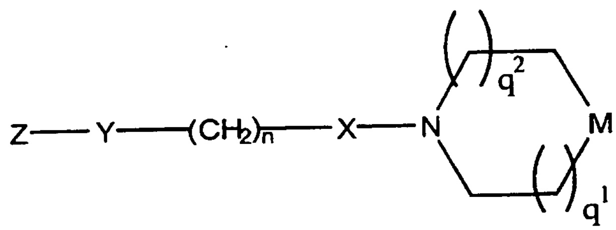
Those skilled in the art will be able to recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments

of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

What is claimed is:

1. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation comprising administering to a subject an effective amount of a compound represented by the following structural formula:



and physiologically acceptable salts thereof, wherein:

Y is a single covalent bond;

n is an integer from one to about four;

X is a single covalent bond;

M is $>NR^2$, $>CR^1R^2$, $-O-CR^1R^2-O-$ or $-CH_2-CR^1R^2-O-$;

The ring containing M is substituted or unsubstituted;

q^1 is an integer, such as an integer from zero to about three;

q^2 is an integer from zero to about one;

R^1 is -H, -OH, $-N_3$, a halogen, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, -O-(aliphatic group), -O-(substituted aliphatic group),-SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group),
-C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -COOH, -CN, $-CO-NR^3R^4$, $-NR^3R^4$ or R^1 is a covalent

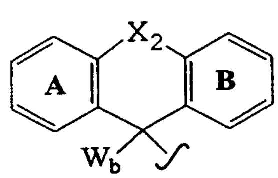
bond between the ring atom at M and an adjacent carbon atom in the ring which contains M;

R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, -O-(substituted or unsubstituted aromatic group) or -O-(substituted or unsubstituted aliphatic group);

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by:



wherein:

W_b is -H, -CH=NH, -CN, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

X_2 is $-S-CH_2-$, $-CH_2-S-$, $-CH_2-O-$, $-O-CH_2-$, $-CO-NR_c-$, $-NR_c-CO-$, $-CH_2-S(O)_2-$, $-S(O)_2-CH_2-$, $-CH_2-NR_c-$, $-NR_c-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-SO-$, $-SO-CH_2-$, $-O-$ or a bond;

R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

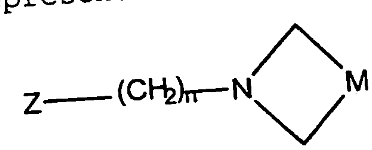
2. The method of Claim 1 wherein

R^1 is $-H$, $-OH$, $-N_3$, $-CN$, a halogen, a substituted aliphatic group, an aminoalkyl group, -O-(aliphatic group), -O-(substituted aliphatic group), $-NR^3R^4$ or R^1 is a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M;

R^2 is $-NR^5R^6$, a substituted acyl group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, -O-(substituted or unsubstituted aromatic group); or

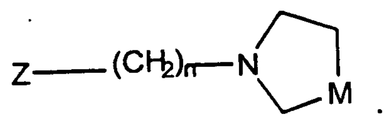
R^1 and R^2 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

3. The method of Claim 1 wherein q^1 and q^2 are zero, and the compound is represented by the structural formula:



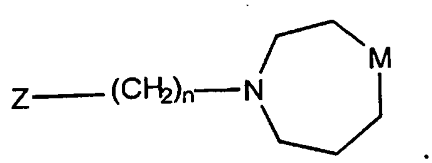
4. The method of Claim 3 wherein M is $>CR^1R^2$.

5. The method of Claim 1 wherein q^1 is one and q^2 is zero, and the compound is represented by the structural formula:



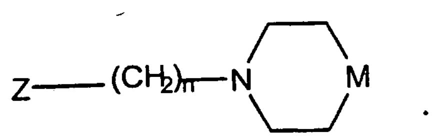
6. The method of Claim 5 wherein M is $>CR^1R^2$.

7. The method of Claim 1 wherein q^1 is one and q^2 is two, and the compound is represented by the structural formula:



8. The method of Claim 7 wherein M is $>NR^2$.

9. The method of Claim 1 wherein q^1 is one and q^2 is two, and the compound is represented by the structural formula:



10. The method of Claim 9 wherein M is $-O-CR^1R^2-O-$ or $-CH_2-CR^1R^2-O-$.

11. The method of Claim 9 wherein:

M is $>NR^2$ or $>CR^1R^2$; and

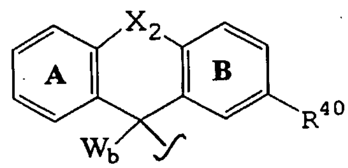
R^1 is a substituted aliphatic group or an aminoalkyl group.

12. The method of Claim 9 wherein:

M is $>NR^2$ or $>CR^1R^2$; and

R^2 is -O-(substituted or unsubstituted aromatic group).

13. The method of Claim 1 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X_2 in ring C, and Z is represented by the structural formula:



wherein R^{40} is -OH, -COOH, $-NO_2$, halogen, aliphatic group, substituted aliphatic group, an aromatic group, a substituted aromatic group, $-NR^{24}R^{25}$, $-CONR^{24}R^{25}$, Q-(aliphatic group), Q-(substituted aliphatic group), -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$;

R^{20}, R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

Q is $-NR^{24}C(O)-$, $-NR^{24}S(O)_2-$ or $-C(O)O-$;

R^{24} and R^{25} are independently -H, -OH, an aliphatic group or a substituted aliphatic group;

u is zero or one; and

t is an integer from zero to about 3.

14. The method of Claim 13 wherein R^{40} is represented by $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$.

15. The method of Claim 14 wherein u is zero and t one to about three.

16. The method of Claim 14 wherein u is one and t is zero.

17. The method of Claim 14 wherein u and t are both zero.

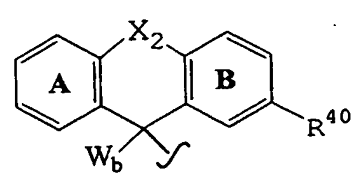
18. The method of Claim 13 wherein R^{40} is a aliphatic group that is substituted with $-NR^{24}R^{25}$ or $-CONR^{24}R^{25}$.

19. The method of Claim 13 wherein R^{40} is -O-(aliphatic group) or -O-(substituted aliphatic group).

20. The method of Claim 13 wherein R^{40} is -COOH.

21. The method of Claim 1 wherein X_1 is $-CH_2-O-$.

22. The method of Claim 1 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X_2 in ring C, and Z is represented by the structural formula:



wherein R^{40} is $-C(=NR^{60})NR^{21}R^{22}$, $-O-C(O)-NR^{21}R^{26}$,

$-S(O)_2-NR^{21}R^{22}$ or $-N-C(O)-NR^{21}R^{22}$; wherein

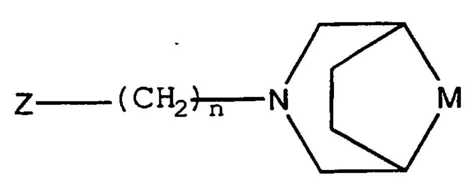
R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring;

R^{26} is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), $-S(O)_2-$(substituted or unsubstituted aliphatic group), $-S(O)_2-$(substituted or unsubstituted aromatic group); or

R^{26} and R^{21}, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

23. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation, comprising administering to a subject in need thereof an effective amount of a compound represented by the following structural formula:



and physiologically acceptable salts thereof, wherein:

n is an integer from one to about four;

M is $>NR^2$, $>CR^1R^2$, $-O-CR^1R^2-O-$ or $-CH_2-CR^1R^2-O-$;

The ring containing M is substituted or unsubstituted;

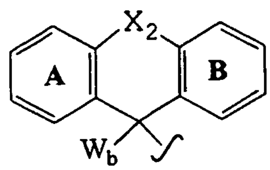
R^1 is -H, -OH, $-N_3$, a halogen, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, -O-(aliphatic group), -O-(substituted aliphatic group),-SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group),
-C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -COOH, -CN, $-CO-NR^3R^4$, $-NR^3R^4$ or R^1 is a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M;

R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group,
-O-(substituted or unsubstituted aromatic group) or
-O-(substituted or unsubstituted aliphatic group);

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by:



wherein:

W_b is -H, -CH=NH, -CN, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

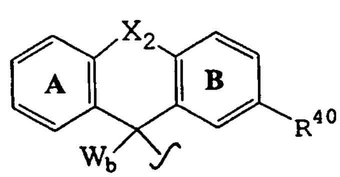
R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

X_2 is $-S-CH_2-$, $-CH_2-S-$, $-CH_2-O-$, $-O-CH_2-$, $-CO-NR_c-$, $-NR_c-CO-$, $-CH_2-S(O)_2-$, $-S(O)_2-CH_2-$, $-CH_2-NR_c-$, $-NR_c-CH_2-$, $-CH_2-CH_2-$, -CH=CH-, $-CH_2-SO-$, $-SO-CH_2-$, -O- or a bond;

R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

24. The method of Claim 23 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X_1 in ring C, and Z is represented by the structural formula:



wherein R^{40} is -OH, -COOH, $-NO_2$, halogen, aliphatic group, substituted aliphatic group, an aromatic group, a substituted aromatic group, $-NR^{24}R^{25}$, $-CONR^{24}R^{25}$, Q-(aliphatic group), Q-(substituted aliphatic group), -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$;

R^{20}, R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

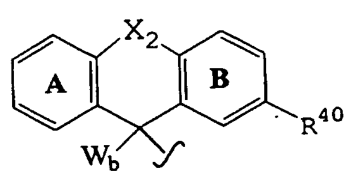
Q is $-NR^{24}C(O)-$, $-NR^{24}S(O)_2-$ or $-C(O)O-$;

R^{24} and R^{25} are independently -H, -OH, an aliphatic group or a substituted aliphatic group;

u is zero or one; and

t is an integer from zero to about 3.

25. The method of Claim 23 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X_2 in ring C, and Z is represented by the structural formula:



wherein R^{40} is $-C(=NR^{60})NR^{21}R^{22}$, $-O-C(O)-NR^{21}R^{26}$, $-S(O)_2-NR^{21}R^{22}$ or $-N-C(O)-NR^{21}R^{22}$; wherein

R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring;

R^{26} is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), $-S(O)_2-$(substituted or unsubstituted aliphatic group), $-S(O)_2-$(substituted or unsubstituted aromatic group); or

R^{26} and R^{21}, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

26. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation, comprising administering to a subject in need thereof an effective amount of a compound represented by the following structural formula:

$$Z-Y-(CH_2)-X-NR^{50}R^{51}$$

and physiologically acceptable salts thereof, wherein:

Y is a single covalent bond;

n is an integer from one to about four;

X is a covalent bond;

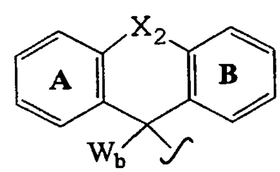
R^{50} and R^{51} are each, independently, -H, an aliphatic group, a substituted aliphatic group, an aminoalkyl

group, $-NR^3R^4$, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group or a covalent bond between the nitrogen atom an adjacent carbon atom;

R^3 and R^4 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^3 and R^4 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by:



wherein:

W_b is -H, -CH=NH, -CN, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

X_2 is $-S-CH_2-$, $-CH_2-S-$, $-CH_2-O-$, $-O-CH_2-$, $-CO-NR_c-$, $-NR_c-CO-$, $-CH_2-S(O)_2-$, $-S(O)_2-CH_2-$, $-CH_2-NR_c-$, $-NR_c-CH_2-$, $-CH_2-CH_2-$, -CH=CH-, $-CH_2-SO-$, $-SO-CH_2-$, -O- or a bond;

R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

27. The method of Claim 26 wherein

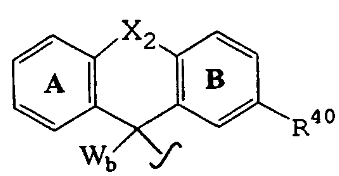
R^{50} is a substituted aliphatic group; and

R^{51} is -H, an aliphatic group or a substituted aliphatic group.

28. The method of Claim 27 wherein R^{50} is an aliphatic group that is substituted with an aromatic group.

29. The method of Claim 27 wherein R^{50} is a aliphatic group that is substituted with a 4-chlorophenyl group.

30. The method of Claim 26 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X_2 in ring C, and Z is represented by the structural formula:



wherein R^{40} is $-C(=NR^{60})NR^{21}R^{22}$, $-O-C(O)-NR^{21}R^{26}$, $-S(O)_2-NR^{21}R^{22}$ or $-N-C(O)-NR^{21}R^{22}$; wherein

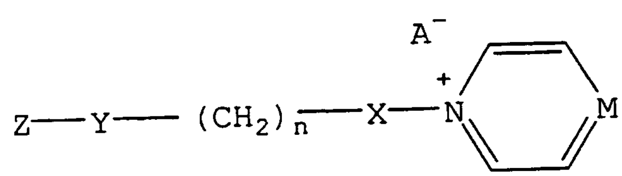
R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring;

R^{26} is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), $-S(O)_2-$(substituted or unsubstituted aliphatic group), $-S(O)_2-$(substituted or unsubstituted aromatic group); or

R^{26} and R^{21}, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

31. A method of treating a disease associated with aberrant leukocyte recruitment and/or activation, comprising administering to a subject in need thereof an effective amount of a compound represented by the following structural formula:



and physiologically acceptable salts thereof, wherein:

Y is a single covalent bond;

n is an integer from one to about four;

X is a single covalent bond;

A^- is a physiologically acceptable anion;

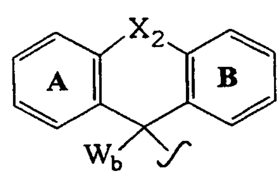
M is $>NR^2$ or $>CR^2$;

R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, -O-(substituted or unsubstituted aromatic group) or -O-(substituted or unsubstituted aliphatic group);

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by:



wherein:

W_b is -H, -CH=NH, -CN, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

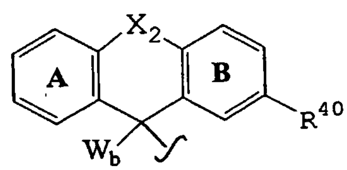
R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

X_2 is -S-CH_2-, -CH_2-S-, -CH_2-O-, -O-CH_2-, -CO-NR_c-, -NR_c-CO-, -CH_2-S(O)$_2$-, -S(O)$_2$-CH_2-, -CH_2-NR_c-, -NR_c-CH_2-, -CH_2-CH_2-, -CH=CH-, -CH_2-SO-, -SO-CH_2-, -O- or a bond;

R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

32. The method of Claim 31 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X_2 in ring C, and Z is represented by the structural formula:



wherein R^{40} is -C(=NR^{60})$NR^{21}R^{22}$, -O-C(O)-$NR^{21}R^{26}$, -S(O)$_2$-$NR^{21}R^{22}$ or -N-C(O)-$NR^{21}R^{22}$; wherein

R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

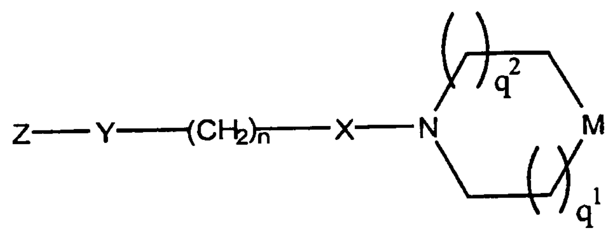
R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring;

R^{26} is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), -S(O)$_2$-(substituted or

unsubstituted aliphatic group), $-S(O)_2-$(substituted or unsubstituted aromatic group); or

R^{26} and R^{21}, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

33. A compound represented by the following structural formula:



or physiologically acceptable salt thereof, wherein:

Y is a single covalent bond;

n is an integer from one to about four;

X is a single covalent bond;

M is $>NR^2$, $>CR^1R^2$, $-O-CR^1R^2-O-$ or $-CH_2-CR^1R^2-O-$;

The ring containing M is substituted or unsubstituted;

q^1 is an integer, such as an integer from zero to about three;

q^2 is an integer from zero to about one;

R^1 is -H, -OH, $-N_3$, a halogen, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, -O-(aliphatic group), -O-(substituted aliphatic group),-SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group),

-C(O)O-(aliphatic oup), -C(O)O-(substituted aliphatic group), -COOH, -CN, $-CO-NR^3R^4$, $-NR^3R^4$ or R^1 is a covalent

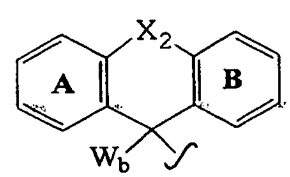
bond between the ring atom at M and an adjacent carbon atom in the ring which contains M;

R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, -O-(substituted or unsubstituted aromatic group) or -O-(substituted or unsubstituted aliphatic group);

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by:



wherein:

W_b is -H, -CH=NH, -CN, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

X_2 is $-S-CH_2-$, $-CH_2-S-$, $-CH_2-O-$, $-O-CH_2-$, $-CO-NR_c-$, $-NR_c-CO-$, $-CH_2-S(O)_2-$, $-S(O)_2-CH_2-$, $-CH_2-NR_c-$, $-NR_c-CH_2-$, $-CH_2-CH_2-$, $-CH{=}CH-$, $-CH_2-SO-$, $-SO-CH_2-$, $-O-$ or a bond;

R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

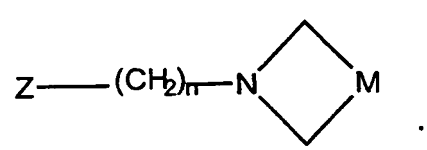
34. The compound of Claim 33 wherein

R^1 is -H, -OH, $-N_3$, -CN, a halogen, a substituted aliphatic group, an aminoalkyl group, -O-(aliphatic group), -O-(substituted aliphatic group), $-NR^3R^4$ or R^1 is a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M;

R^2 is $-NR^5R^6$, a substituted acyl group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, -O-(substituted or unsubstituted aromatic group); or

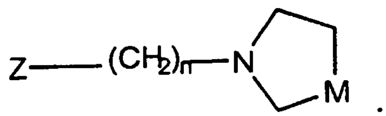
R^1 and R^2 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring.

35. The compound of Claim 33 wherein q^1 and q^2 are zero, and the compound is represented by the structural formula:



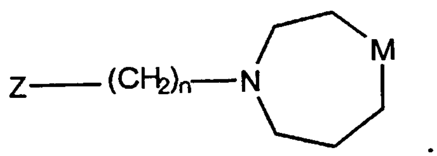
36. The compound of Claim 35 wherein M is $>CR^1R^2$.

37. The compound of Claim 33 wherein q^1 is one and q^2 is zero, and the compound is represented by the structural formula:



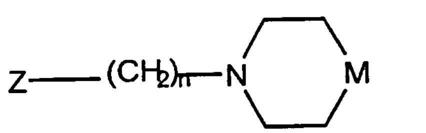
38. The compound of Claim 37 wherein M is >CR^1R^2.

39. The compound of Claim 33 wherein q^1 is one and q^2 is two, and the compound is represented by the structural formula:



40. The compound of Claim 39 wherein M is >NR^2.

41. The compound of Claim 33 wherein q^1 is one and q^2 is two, and the compound is represented by the structural formula:



42. The compound of Claim 41 wherein M is $-O-CR^1R^2-O-$ or $-CH_2-CR^1R^2-O-$.

43. The compound of Claim 41 wherein:

M is >NR^2 or >CR^1R^2; and

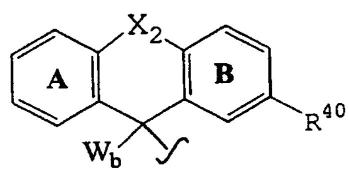
R^1 is a substituted aliphatic group or an aminoalkyl group.

44. The compound of Claim 41 wherein:

M is $>NR^2$ or $>CR^1R^2$; and

R^2 is -O-(substituted or unsubstituted aromatic group).

45. The compound of Claim 33 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X_2 in ring C, and Z is represented by the structural formula:



wherein R^{40} is -OH, -COOH, $-NO_2$, halogen, aliphatic group, substituted aliphatic group, an aromatic group, a substituted aromatic group, $-NR^{24}R^{25}$, $-CONR^{24}R^{25}$, Q-(aliphatic group), Q-(substituted aliphatic group), -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$;

R^{20}, R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

Q is $-NR^{24}C(O)-$ or $-NR^{24}S(O)_2-$;

R^{24} and R^{25} are independently -H, -OH, an aliphatic group or a substituted aliphatic group;

u is zero or one; and

t is an integer from zero to about 3.

46. The compound of Claim 45 wherein R^{40} is represented by $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$.

47. The compound of Claim 46 wherein u is zero and t one to about three.

48. The compound of Claim 46 wherein u is one and t is zero.

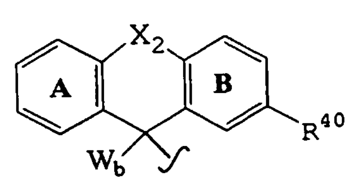
49. The compound of Claim 46 wherein u and t are both zero.

50. The compound of Claim 45 wherein R^{40} is a aliphatic group that is substituted with $-NR^{24}R^{25}$ or $-CONR^{24}R^{25}$.

51. The compound of Claim 45 wherein R^{40} is -O-(aliphatic group) or -O-(substituted aliphatic group).

52. The compound of Claim 45 wherein R^{40} is -COOH.

53. The compound of Claim 33 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X_2 in ring C, and Z is represented by the structural formula:



wherein R^{40} is $-C(=NR^{60})NR^{21}R^{22}$, $-O-C(O)-NR^{21}R^{26}$, $-S(O)_2-NR^{21}R^{22}$ or $-N-C(O)-NR^{21}R^{22}$; wherein

R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

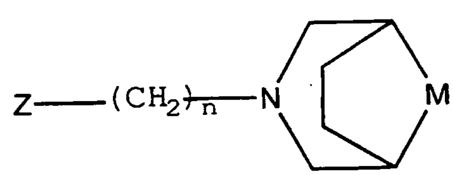
R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring;

R^{26} is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), $-S(O)_2-$(substituted or unsubstituted aliphatic group), $-S(O)_2-$(substituted or unsubstituted aromatic group); or

R^{26} and R^{21}, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

54. The compound of Claim 33 wherein X_1 is $-CH_2-O-$.

55. A compound represented by the following structural formula:



or physiologically acceptable salt thereof, wherein:

n is an integer from one to about four;

M is $>NR^2$, $>CR^1R^2$, $-O-CR^1R^2-O-$ or $-CH_2-CR^1R^2-O-$;

The ring containing M is substituted or unsubstituted;

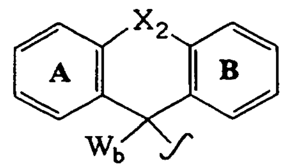
R^1 is -H, -OH, $-N_3$, a halogen, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, -O-(aliphatic group), -O-(substituted aliphatic group),-SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -COOH, -CN, $-CO-NR^3R^4$, $-NR^3R^4$ or R^1 is a covalent bond between the ring atom at M and an adjacent carbon atom in the ring which contains M;

R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, -O-(substituted or unsubstituted aromatic group) or -O-(substituted or unsubstituted aliphatic group);

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by:



wherein:

W_b is -H, -CH=NH, -CN, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

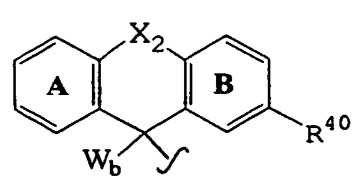
R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

X_2 is $-S-CH_2-$, $-CH_2-S-$, $-CH_2-O-$, $-O-CH_2-$, $-CO-NR_c-$, $-NR_c-CO-$, $-CH_2-S(O)_2-$, $-S(O)_2-CH_2-$, $-CH_2-NR_c-$, $-NR_c-CH_2-$, $-CH_2-CH_2-$, -CH=CH-, $-CH_2-SO-$, $-SO-CH_2-$, -O- or a bond;

R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

56. The compound of Claim 55 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X_1 in ring C, and Z is represented by the structural formula:



wherein R^{40} is $-OH$, $-COOH$, $-NO_2$, halogen, aliphatic group, substituted aliphatic group, an aromatic group, a substituted aromatic group, $-NR^{24}R^{25}$, $-CONR^{24}R^{25}$, Q-(aliphatic group), Q-(substituted aliphatic group), -O-(aliphatic group), -O-(substituted aliphatic group), -O-(aromatic group), -O-(substituted aromatic group), an electron withdrawing group, $-(O)_u-(CH_2)_t-C(O)OR^{20}$, $-(O)_u-(CH_2)_t-OC(O)R^{20}$, $-(O)_u-(CH_2)_t-C(O)-NR^{21}R^{22}$ or $-(O)_u-(CH_2)_t-NHC(O)O-R^{20}$;

R^{20}, R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

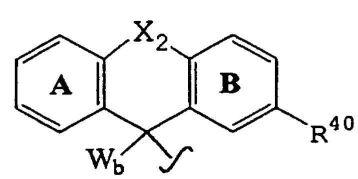
Q is $-NR^{24}C(O)-$, $-NR^{24}S(O)_2-$ or $-C(O)O-$;

R^{24} and R^{25} are independently -H, -OH, an aliphatic group or a substituted aliphatic group;

u is zero or one; and

t is an integer from zero to about 3.

57. The compound of Claim 56 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X_2 in ring C, and Z is represented by the structural formula:



wherein R^{40} is $-C(=NR^{60})NR^{21}R^{22}$, $-O-C(O)-NR^{21}R^{26}$, $-S(O)_2-NR^{21}R^{22}$ or $-N-C(O)-NR^{21}R^{22}$; wherein

R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring;

R^{26} is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), $-S(O)_2-$(substituted or unsubstituted aliphatic group), $-S(O)_2-$(substituted or unsubstituted aromatic group); or

R^{26} and R^{21}, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

58. A compound represented by the following structural formula:

$$Z-Y-(CH_2)-X-NR^{50}R^{51}$$

or physiologically acceptable salt thereof, wherein:

Y is a single covalent bond;

n is an integer from one to about four;

X is a covalent bond;

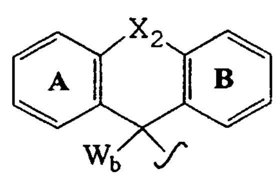
R^{50} and R^{51} are each, independently, -H, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, $-NR^3R^4$, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-

aromatic heterocyclic group or a covalent bond between the nitrogen atom an adjacent carbon atom;

R^3 and R^4 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^3 and R^4 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by:



wherein:

W_b is -H, -CH=NH, -CN, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

X_2 is $-S-CH_2-$, $-CH_2-S-$, $-CH_2-O-$, $-O-CH_2-$, $-CO-NR_c-$, $-NR_c-CO-$, $-CH_2-S(O)_2-$, $-S(O)_2-CH_2-$, $-CH_2-NR_c-$, $-NR_c-CH_2-$, $-CH_2-CH_2-$, -CH=CH-, $-CH_2-SO-$, $-SO-CH_2-$, -O- or a bond;

R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted

aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

59. The compound of Claim 58 wherein

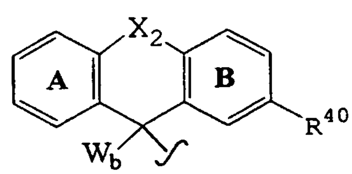
R^{50} is a substituted aliphatic group; and

R^{51} is -H, an aliphatic group or a substituted aliphatic group.

60. The compound of Claim 59 wherein R^{50} is an aliphatic group that is substituted with an aromatic group.

61. The compound of Claim 59 wherein R^{50} is a aliphatic group that is substituted with a 4-chlorophenyl group.

62. The compound of Claim 58 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X_2 in ring C, and Z is represented by the structural formula:



wherein R^{40} is $-C(=NR^{60})NR^{21}R^{22}$, $-O-C(O)-NR^{21}R^{26}$, $-S(O)_2-NR^{21}R^{22}$ or $-N-C(O)-NR^{21}R^{22}$; wherein

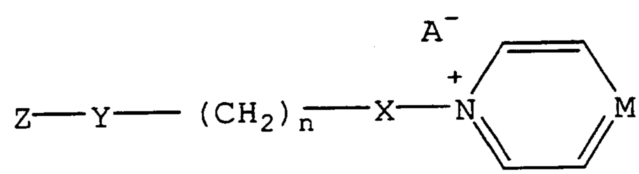
R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring;

R^{26} is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), $-S(O)_2-$(substituted or unsubstituted aliphatic group), $-S(O)_2-$(substituted or unsubstituted aromatic group); or

R^{26} and R^{21}, taken together with the nitrogen atom to which they are bonded, can form a substituted or unsubstituted non-aromatic heterocyclic ring.

63. A compound represented by the following structural formula:



or physiologically acceptable salt thereof, wherein:

Y is a single covalent bond;

n is an integer from one to about four;

X is a single covalent bond;

A^- is a physiologically acceptable anion;

M is $>NR^2$ or $>CR^2$;

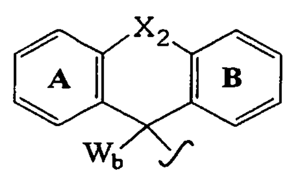
R^2 is -H, -OH, an acyl group, a substituted acyl group, $-NR^5R^6$, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, -O-(substituted or unsubstituted aromatic group) or

-O-(substituted or unsubstituted aliphatic group);

R^3, R^4, R^5 and R^6 are independently -H, an acyl group, a substituted acyl group, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group or a substituted non-aromatic heterocyclic group; or

R^1 and R^2, R^3 and R^4, or R^5 and R^6 taken together with the atom to which they are bonded, form a substituted or unsubstituted non-aromatic carbocyclic or heterocyclic ring;

Z is represented by:



wherein:

W_b is -H, -CH=NH, -CN, $-CH_2-NR^{11}R^{12}$, $-CH_2-OR^{11}$, $-CH_2-NH-CO-NR^{11}R^{12}$, $-CH_2-O-CO-NR^{11}R^{12}$ or $-CH_2-NHC(O)-O-R^{11}$;

R^{11} and R^{12} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{11} and R^{12}, taken together with the nitrogen atom to which they are bonded, form a non-aromatic heterocyclic ring;

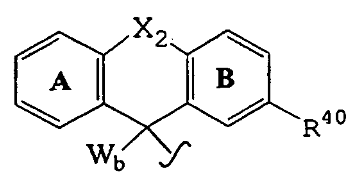
X_2 is $-S-CH_2-$, $-CH_2-S-$, $-CH_2-O-$, $-O-CH_2-$, $-CO-NR_c-$, $-NR_c-CO-$, $-CH_2-S(O)_2-$, $-S(O)_2-CH_2-$, $-CH_2-NR_c-$, $-NR_c-CH_2-$, $-CH_2-CH_2-$, -CH=CH-, $-CH_2-SO-$, $-SO-CH_2-$, -O- or a bond;

R_c is hydrogen, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted

aromatic group, a benzyl group or a substituted benzyl group; and

Ring A and Ring B are independently substituted or unsubstituted.

64. The compound of Claim 63 wherein ring B is substituted para to the carbon atom of ring B that is bonded to X_2 in ring C, and Z is represented by the structural formula:



wherein R^{40} is $-C(=NR^{60})NR^{21}R^{22}$, $-O-C(O)-NR^{21}R^{26}$, $-S(O)_2-NR^{21}R^{22}$ or $-N-C(O)-NR^{21}R^{22}$; wherein

R^{21} and R^{22} are independently -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group or a non-aromatic heterocyclic group; or

R^{21} and R^{22}, taken together with the nitrogen atom to which they are bonded, form a substituted or unsubstituted non-aromatic heterocyclic ring;

R^{26} is -H, an aliphatic group, a substituted aliphatic group, an aromatic group, a substituted aromatic group, a non-aromatic heterocyclic group, -C(O)-O-(substituted or unsubstituted aliphatic group), -C(O)-O-(substituted or unsubstituted aromatic group), $-S(O)_2-$(substituted or unsubstituted aliphatic group), $-S(O)_2-$(substituted or unsubstituted aromatic group); or

R^{26} and R^{21}, taken together with the nitrogen atom to which they are bonded, can form a

substituted or unsubstituted non-aromatic heterocyclic ring.

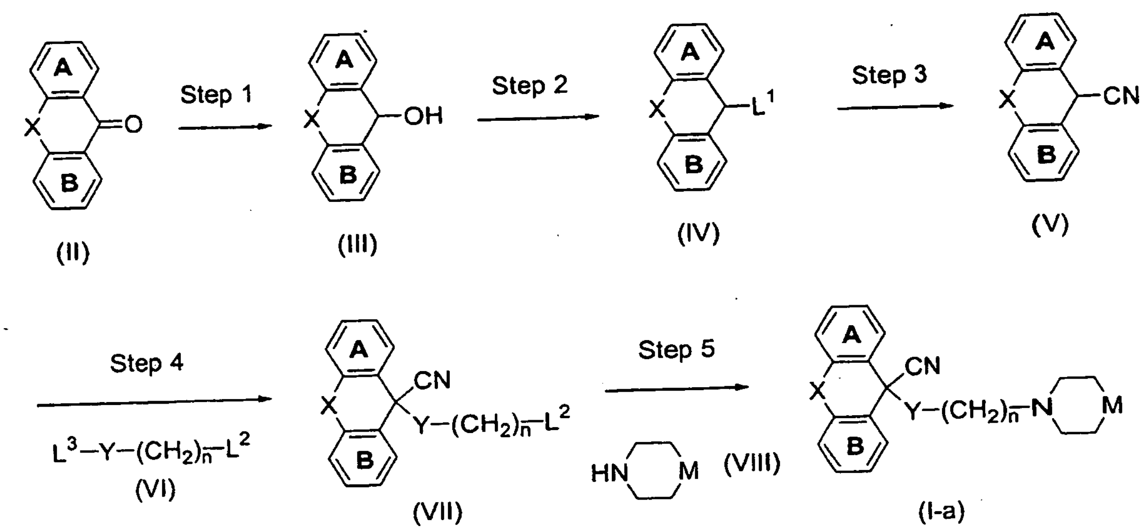


Figure 1

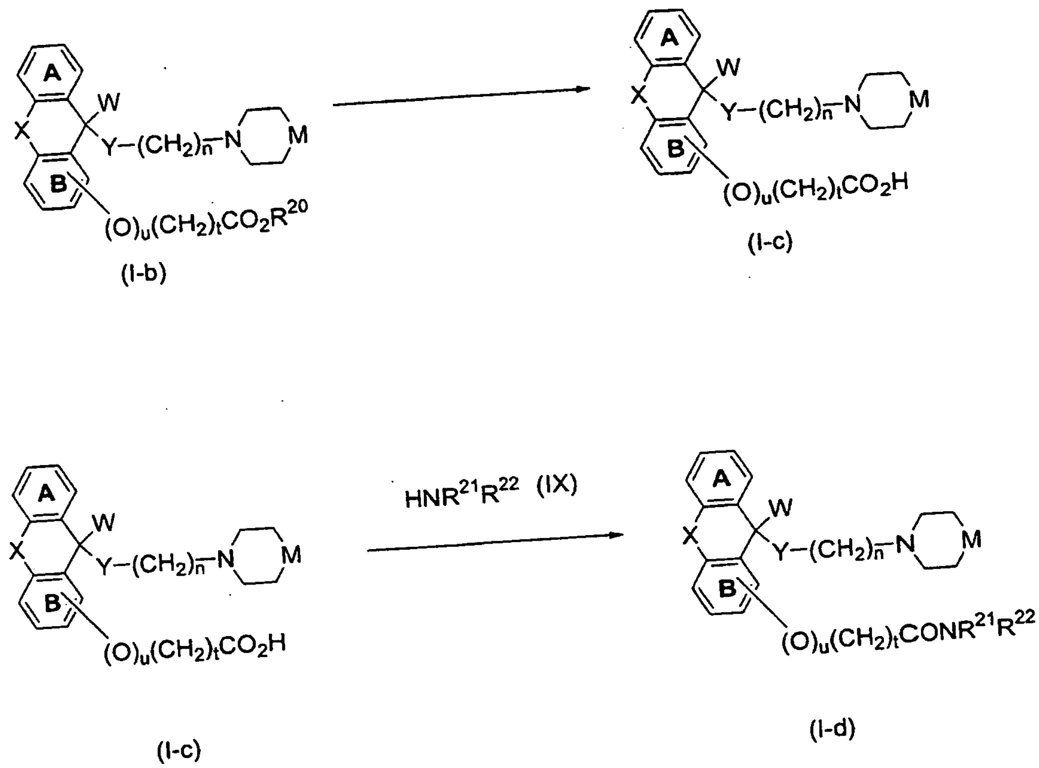
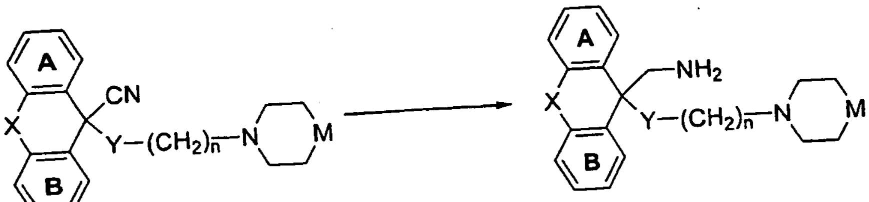
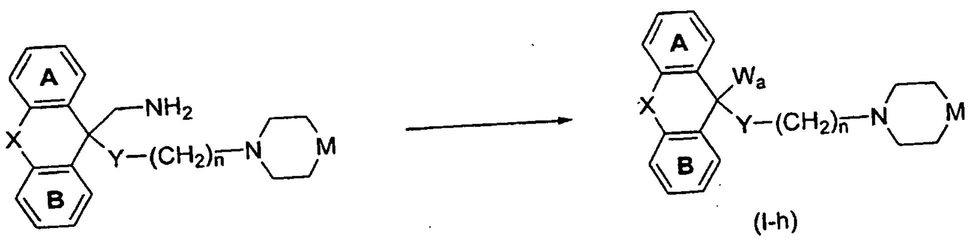

A
B
W
X
Y–(CH2)n–N
M
(O)u(CH2)tCO2R20
(I-b)
(O)u(CH2)tCO2H
(I-c)
HNR21R22 (IX)
(O)u(CH2)tCONR21R22
(I-d)

Figure 2

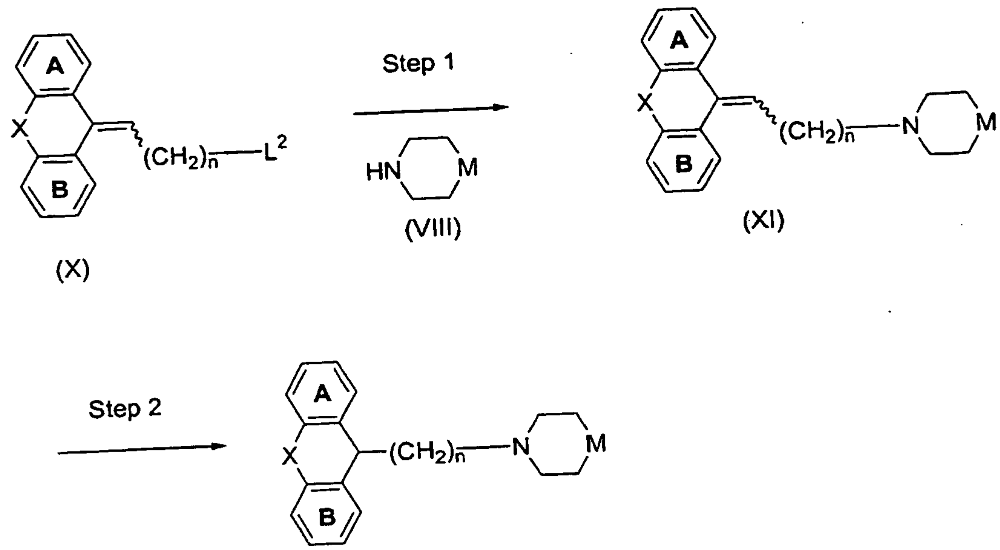


(I-e) (I-f)



(I-f) (I-h)

Figure 3



(X)

(XI)

(I-i)

Figure 4

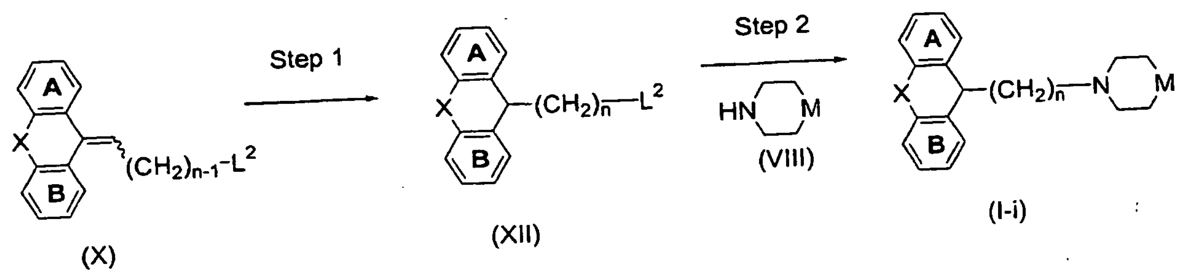
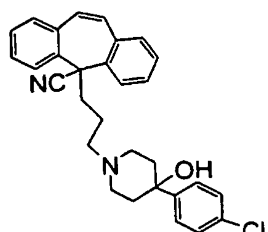
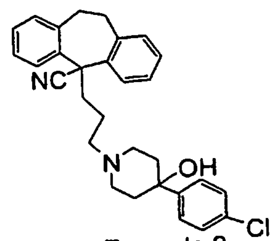


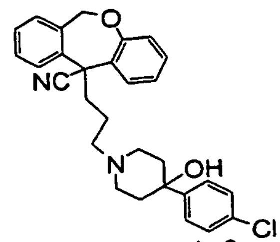
Figure 5



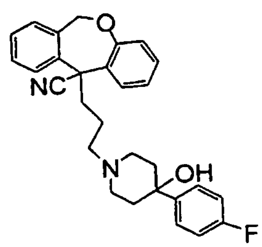
Example 1



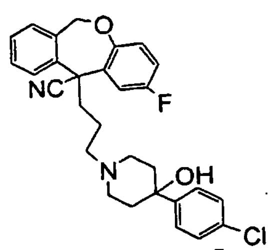
Example 2



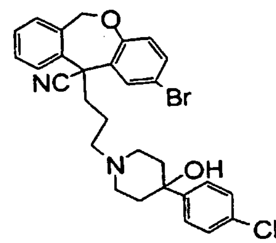
Example 3



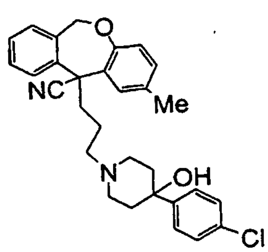
Example 4



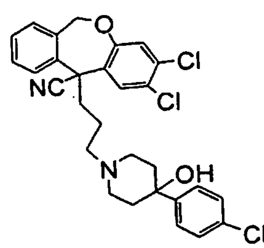
Example 5



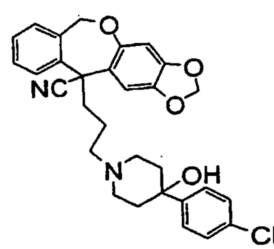
Example 6



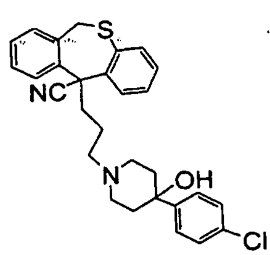
Example 7



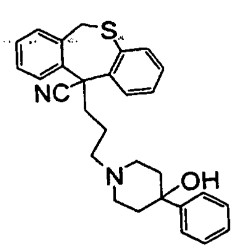
Example 8



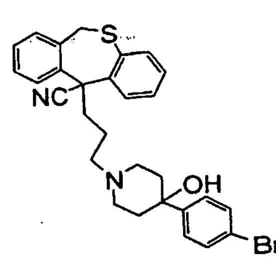
Example 9



Example 10

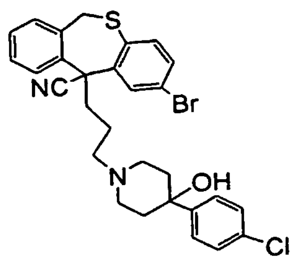


Example 11

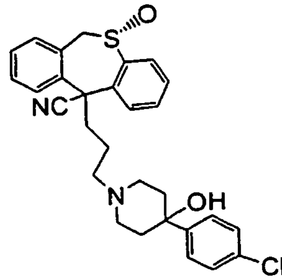


Example 12

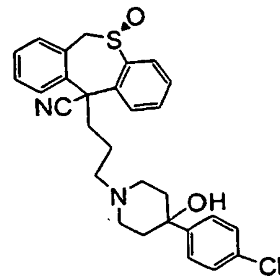
Figure 6A



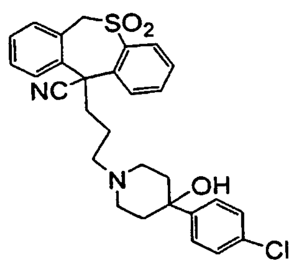
Example 13



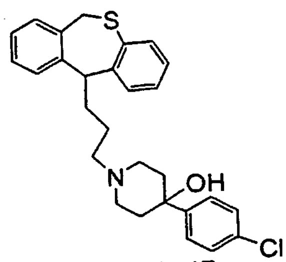
Example 14



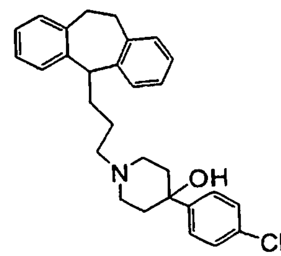
Example 15



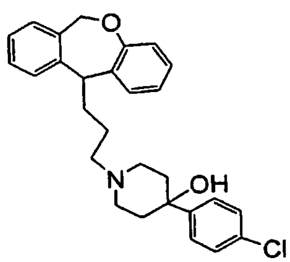
Example 16



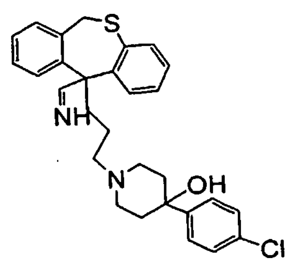
Example 17



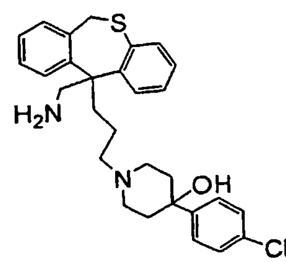
Example 18



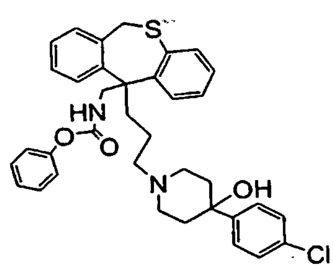
Example 19



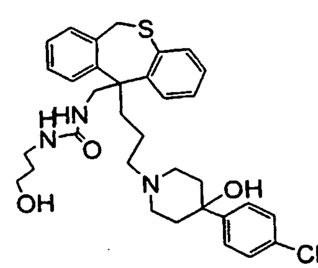
Example 20



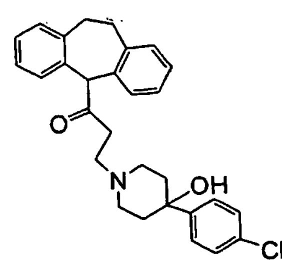
Example 21



Example 22

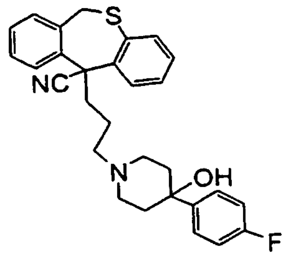


Example 23

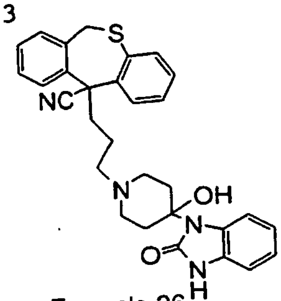


Example 24

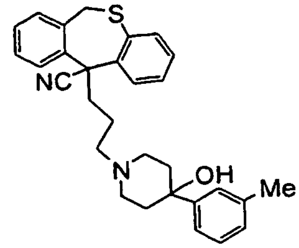
Figure 6B



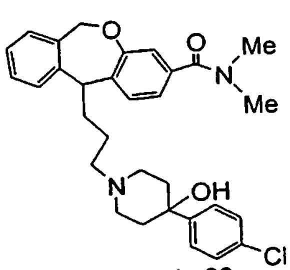
Example 25



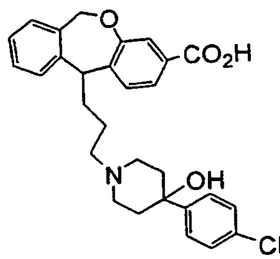
Example 26



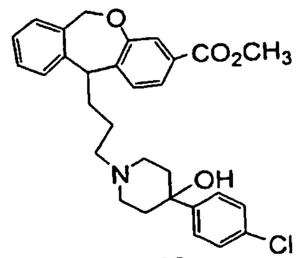
Example 27



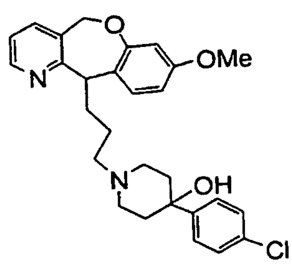
Example 28



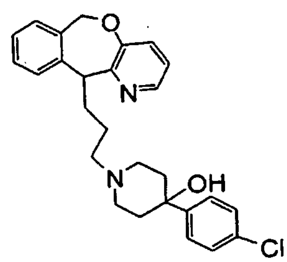
Example 29



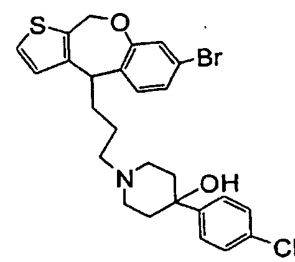
Example 30



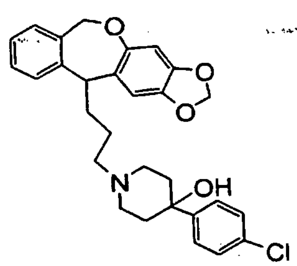
Example 31



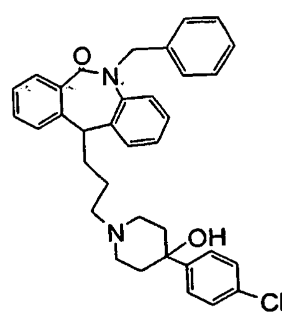
Example 32



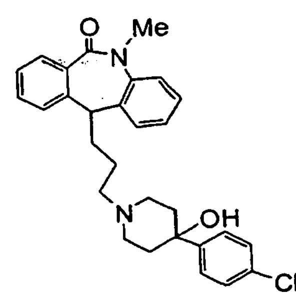
Example 33



Example 34

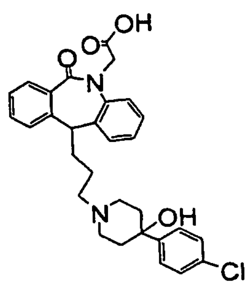


Example 35

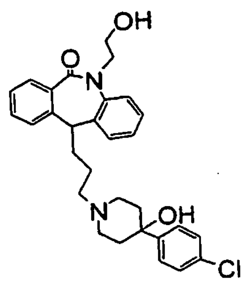


Example 36

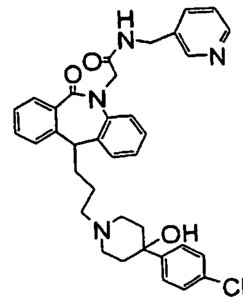
Figure 6C



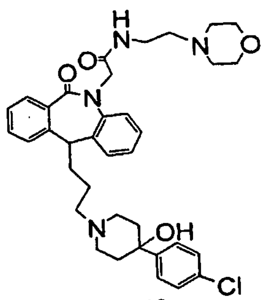
Example 37



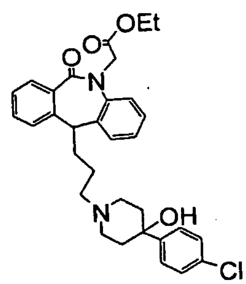
Example 38



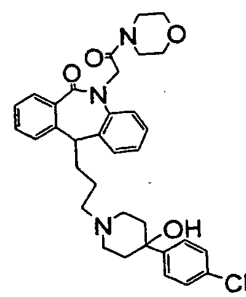
Example 39



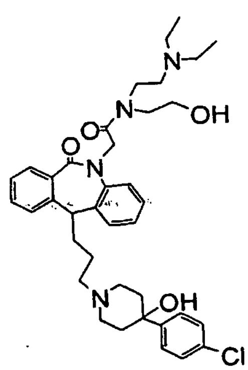
Example 40



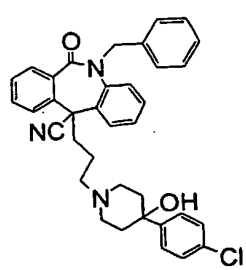
Example 41



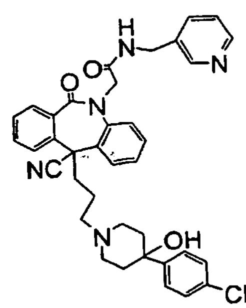
Example 42



Example 43

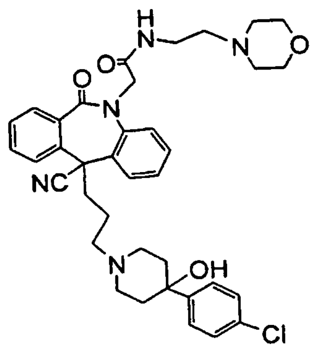


Example 44

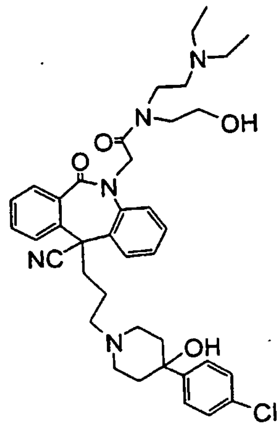


Example 45

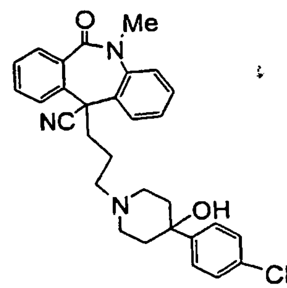
Figure 6D



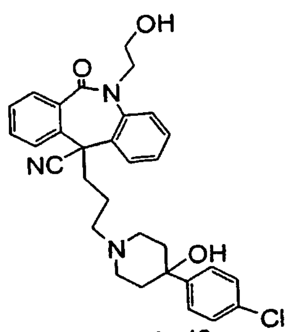
Example 46



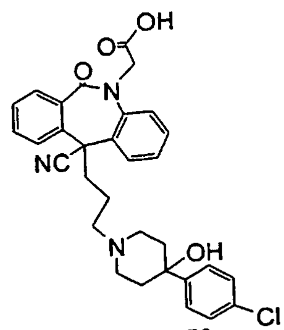
Example 47



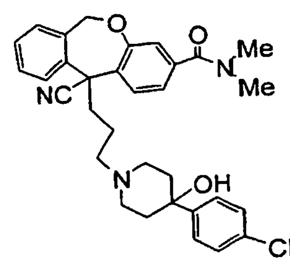
Example 48



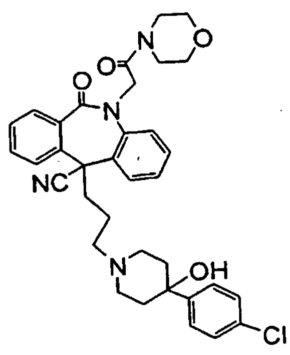
Example 49



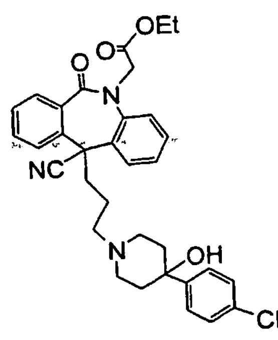
Example 50



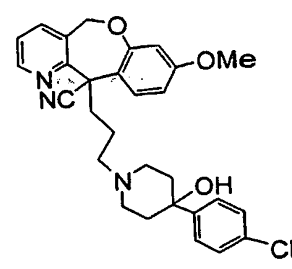
Example 51



Example 52

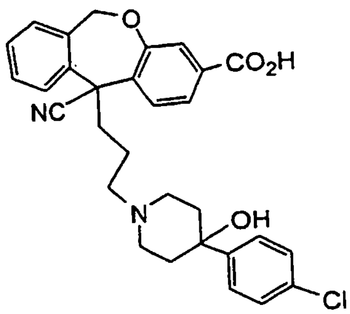


Example 53

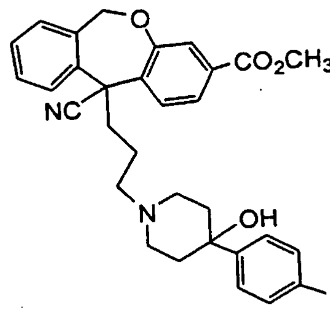


Example 54

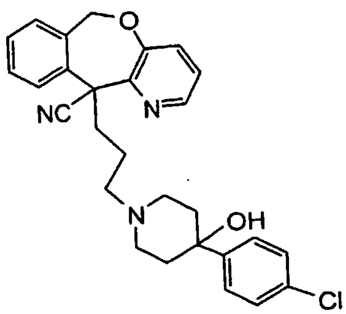
Figure 6E



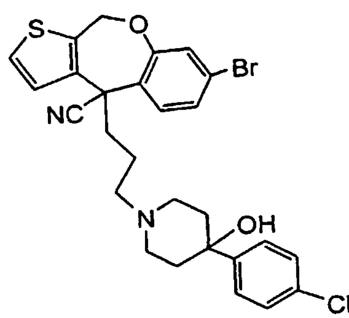
Example 55



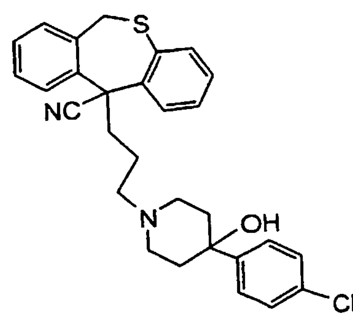
Example 56



Example 57

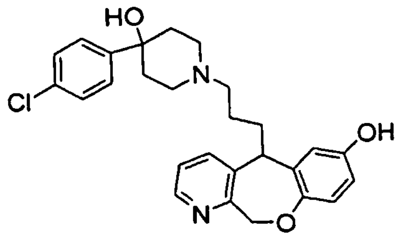


Example 58

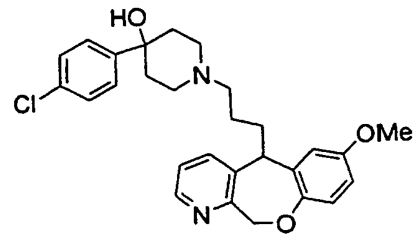


Example 59

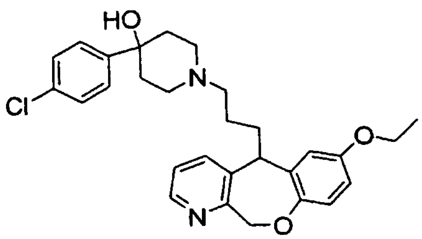
Figure 6F



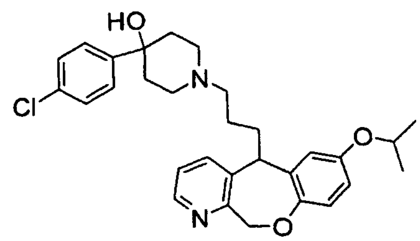
Example 61



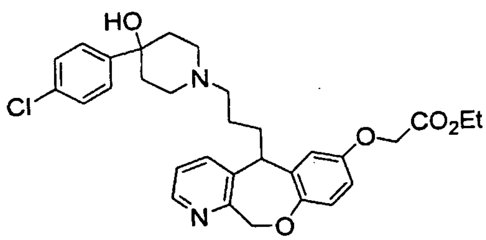
Example 62



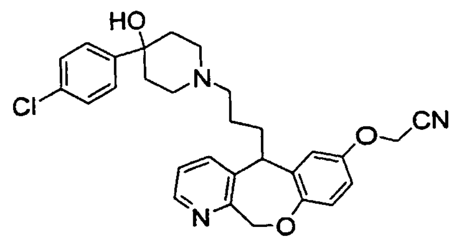
Example 63



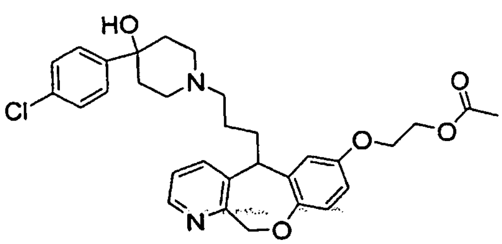
Example 64



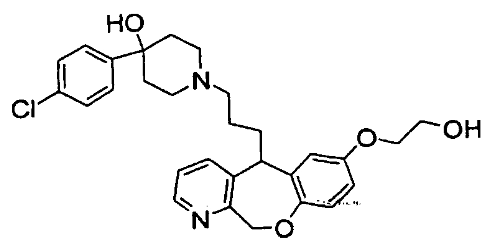
Example 65



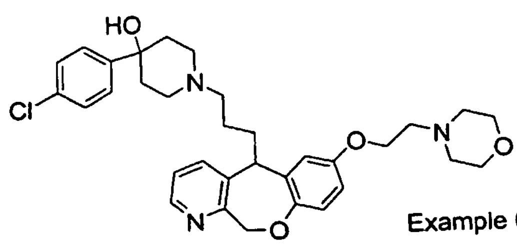
Example 66



Example 67

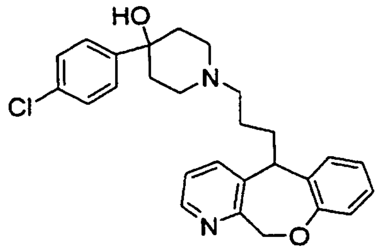


Example 68

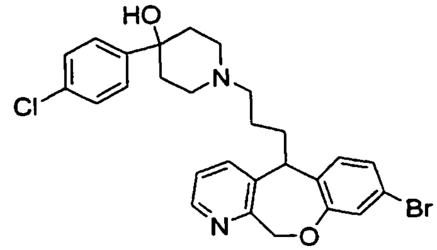


Example 69

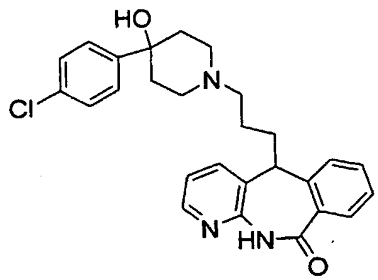
Figure 6G



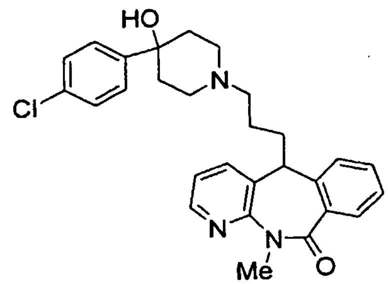
Example 70



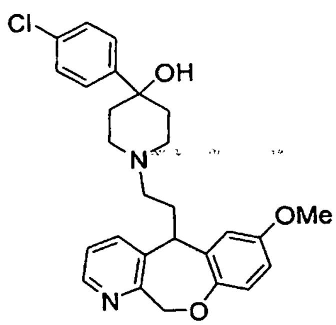
Example 71



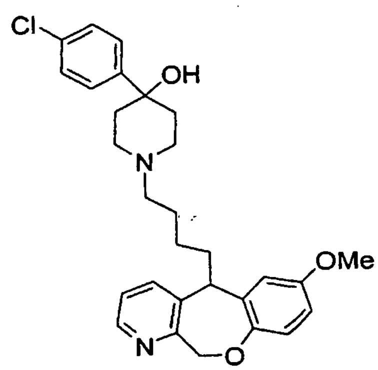
Example 72



Example 73

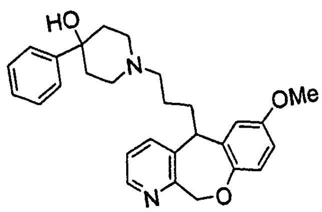


Example 74

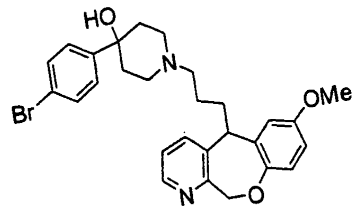


Example 75

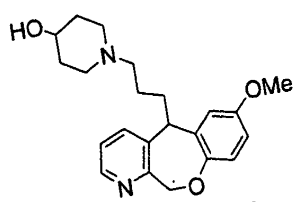
Figure 6H



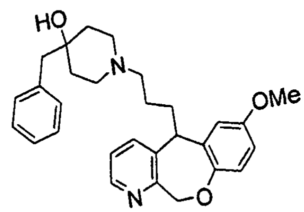
Example 76



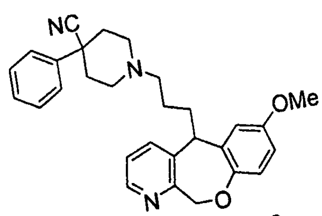
Example 77



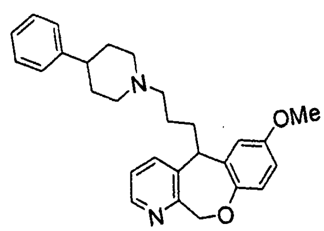
Example 78



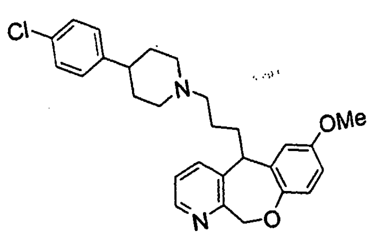
Example 79



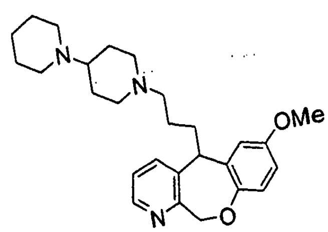
Example 80



Example 81

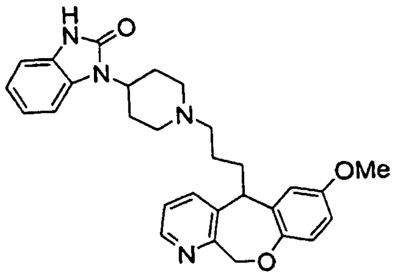


Example 82

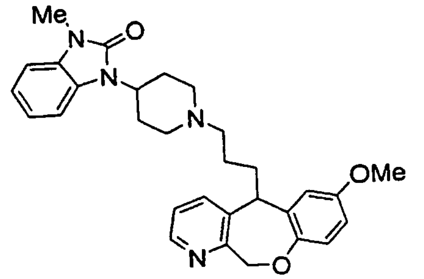


Example 83

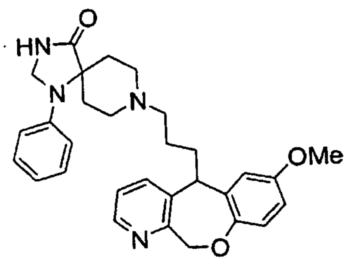
Figure 6I



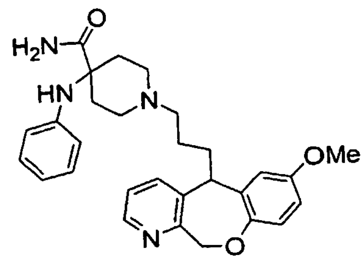
Example 84



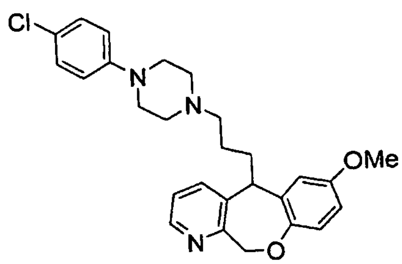
Example 85



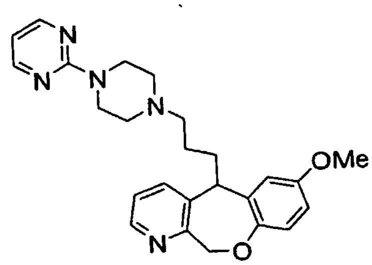
Example 86



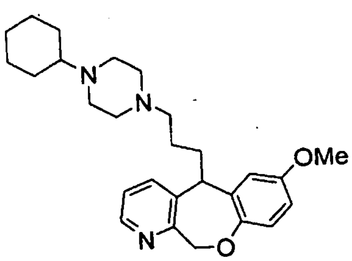
Example 87



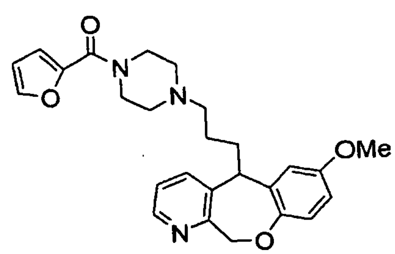
Example 88



Example 89

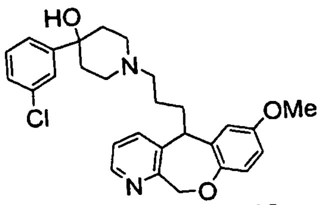


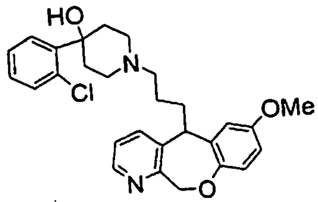
Example 90

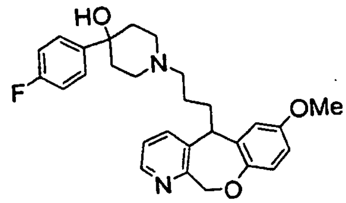


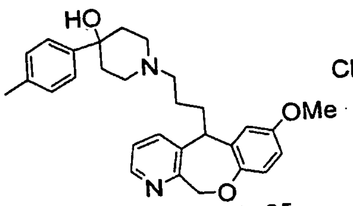
Example 91

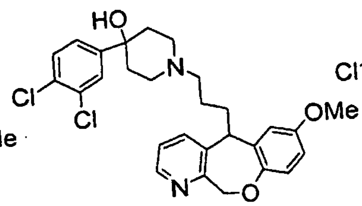
Figure 6J

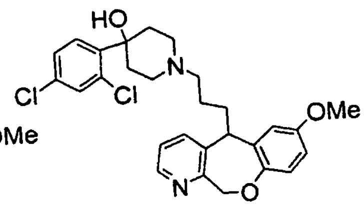

Example 92

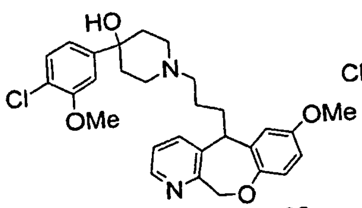

Example 93

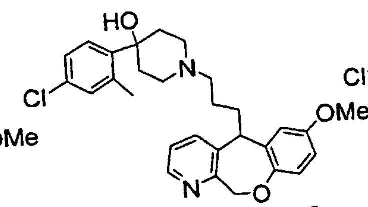

Example 94

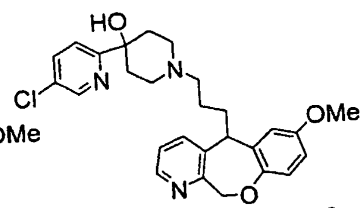

Example 95

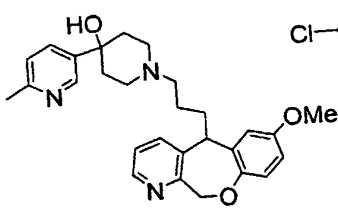

Example 96

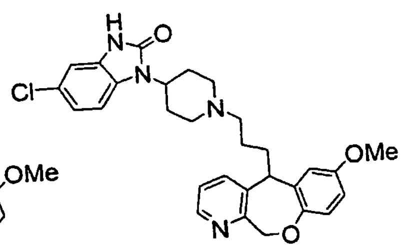

Example 97

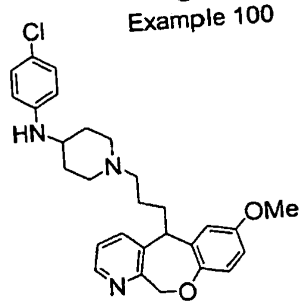

Example 98

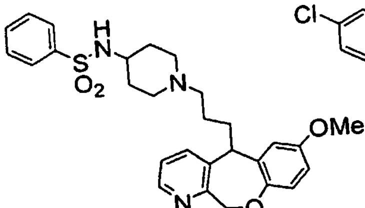

Example 99

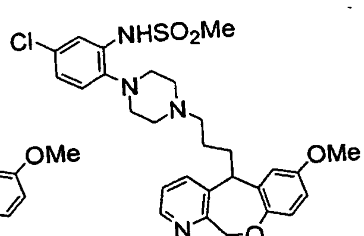

Example 100


Example 101


Example 102


Example 103


Example 104


Example 105

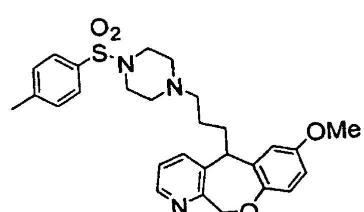
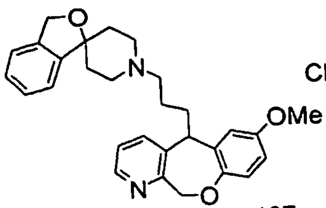
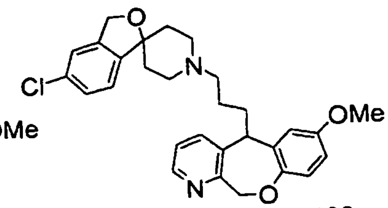
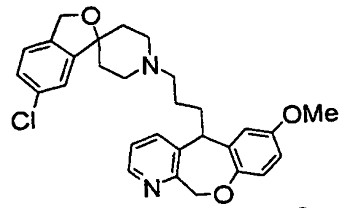
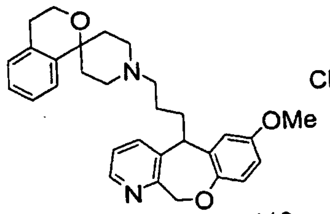

Example 106

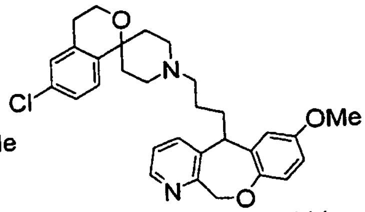
Figure 6K

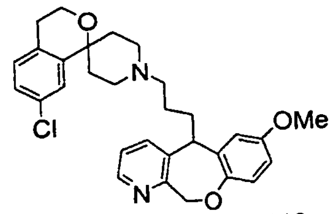

Example 107

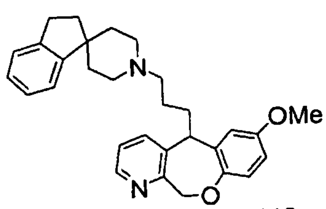

Example 108

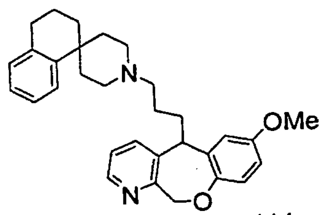

Example 109

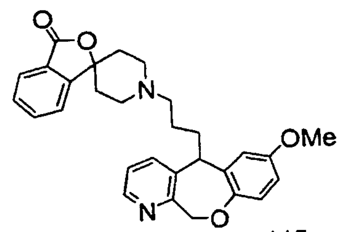

Example 110

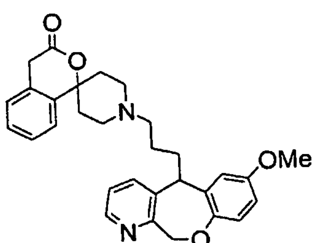

Example 111

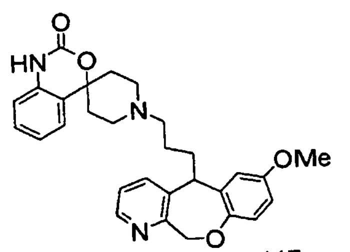

Example 112

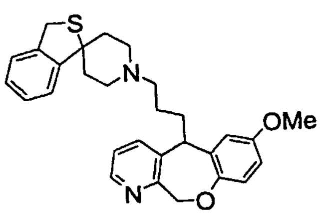

Example 113


Example 114


Example 115


Example 116


Example 117


Example 118

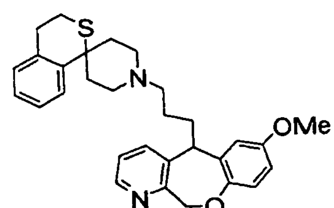
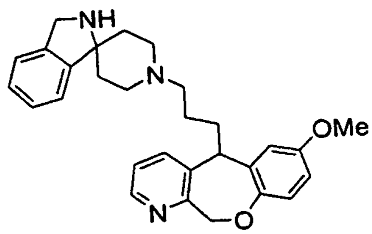
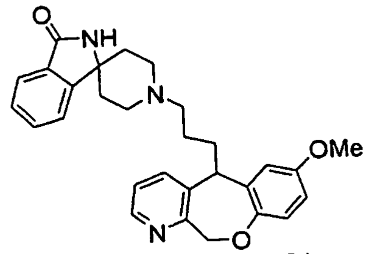

Example 119

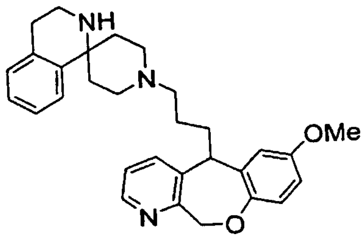
Figure 6L



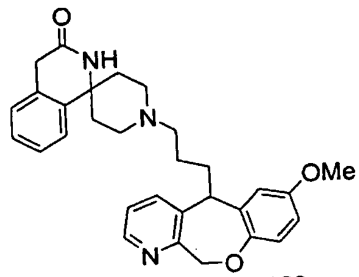
Example 120



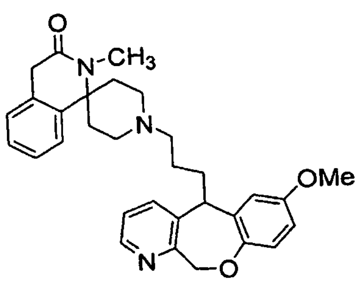
Example 121



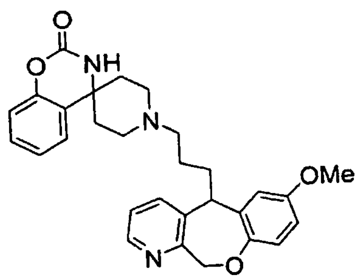
Example 122



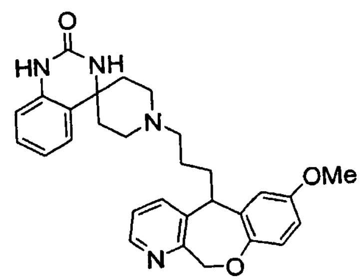
Example 123



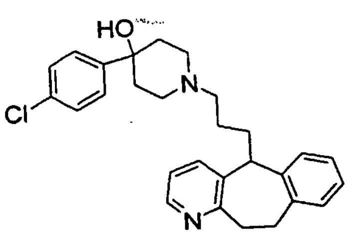
Example 124



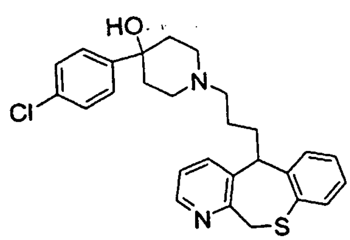
Example 125



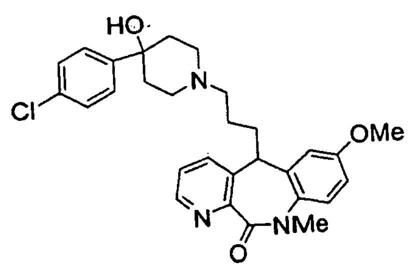
Example 126



Example 127

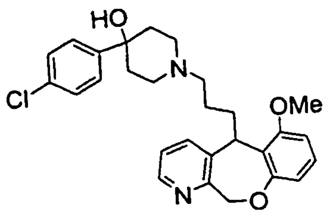


Example 128

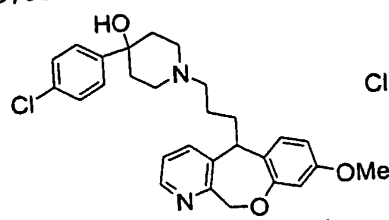


Example 129

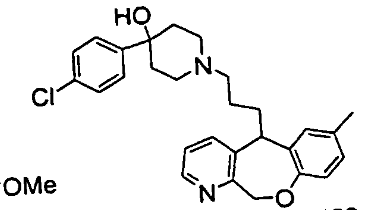
Figure 6M



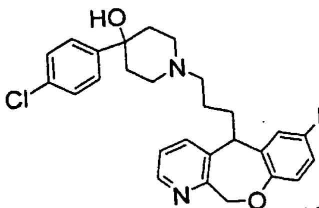
Example 130



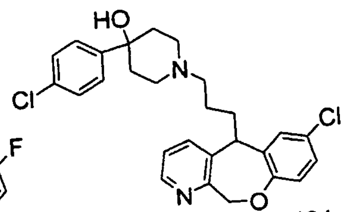
Example 131



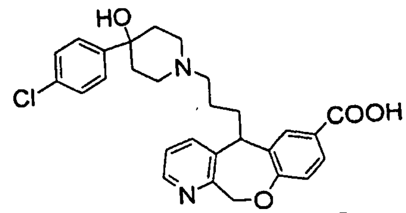
Example 132



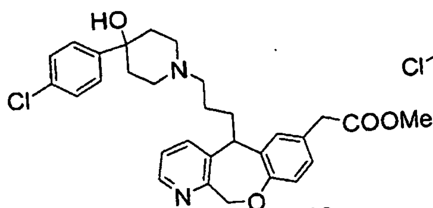
Example 133



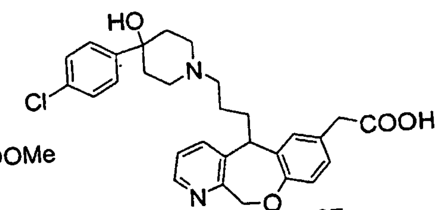
Example 134



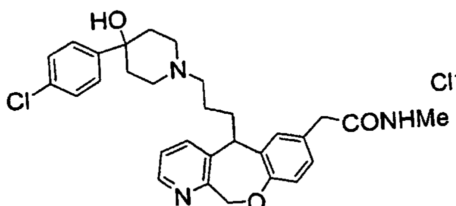
Example 135



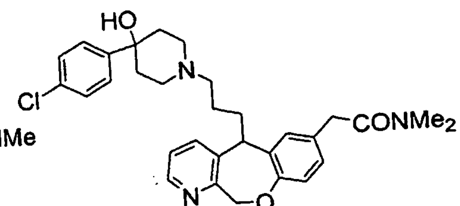
Example 136



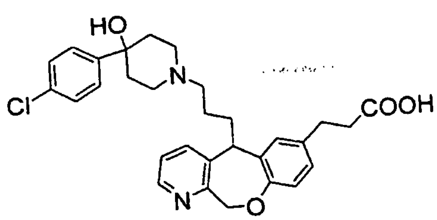
Example 137



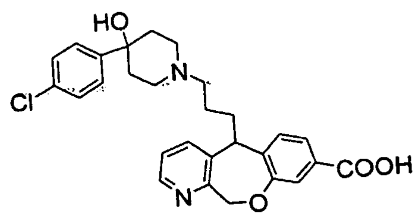
Example 138



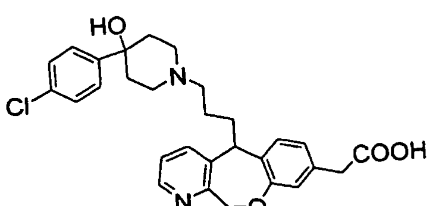
Example 139



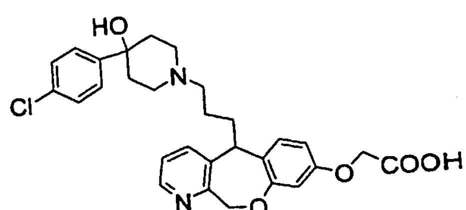
Example 140



Example 141

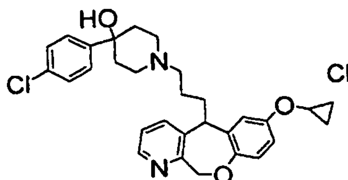


Example 142

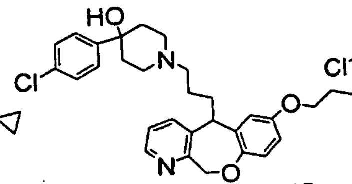


Example 143

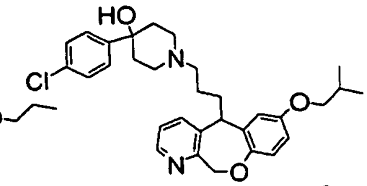
Figure 6N



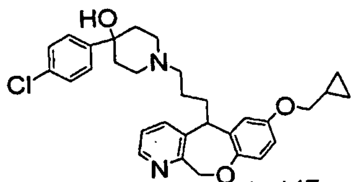
Example 144



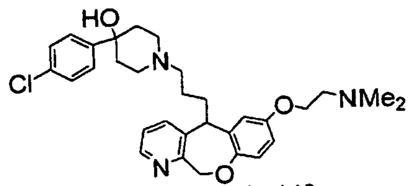
Example 145



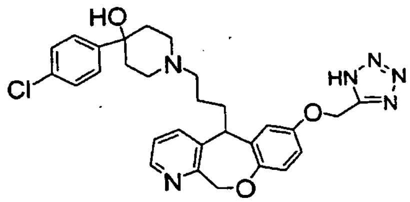
Example 146



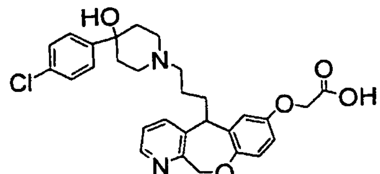
Example 147



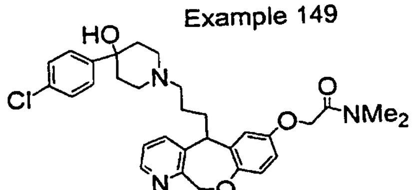
Example 148



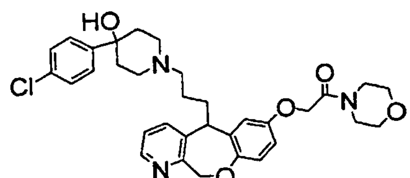
Example 149



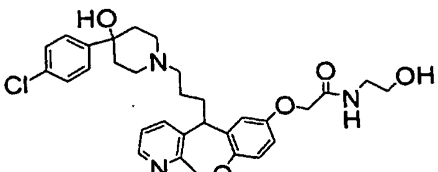
Example 150



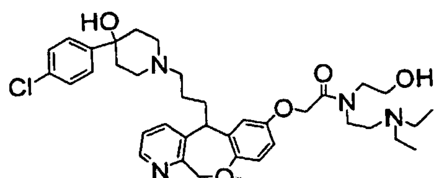
Example 151



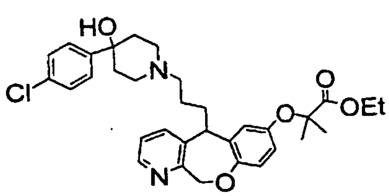
Example 152



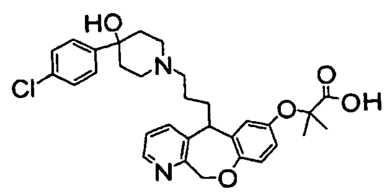
Example 153



Example 154

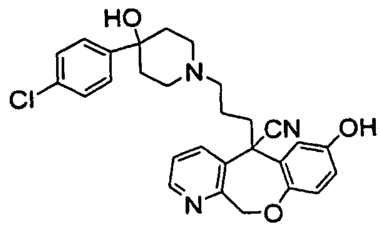


Example 155

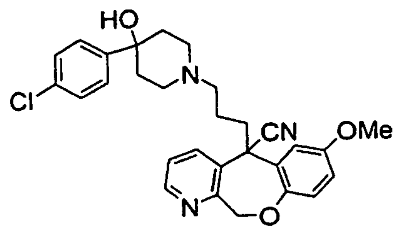


Example 156

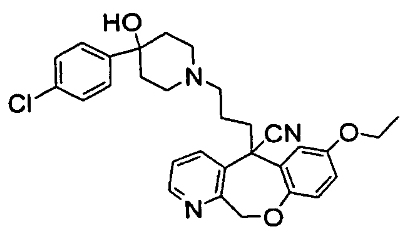
Figure 60



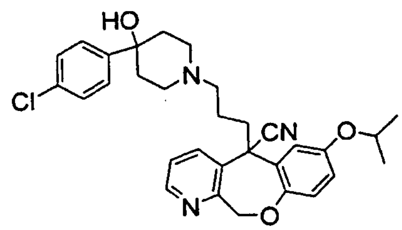
Example 157



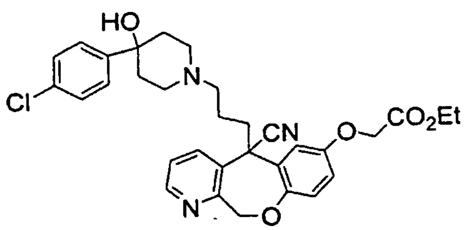
Example 158



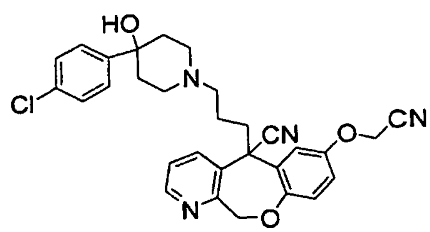
Example 159



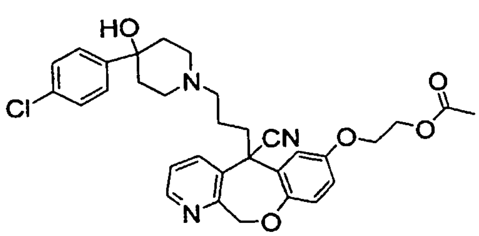
Example 160



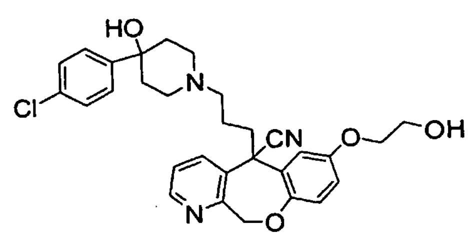
Example 161



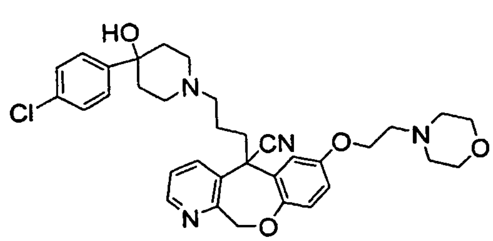
Example 162



Example 163

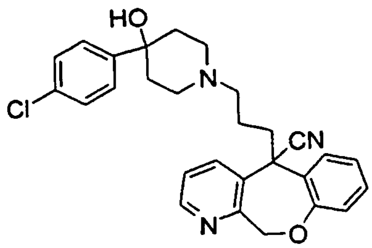


Example 164

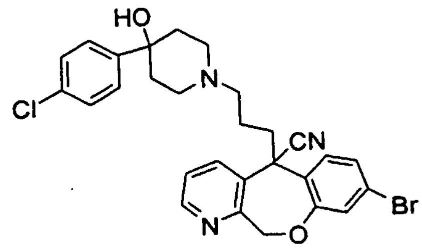


Example 165

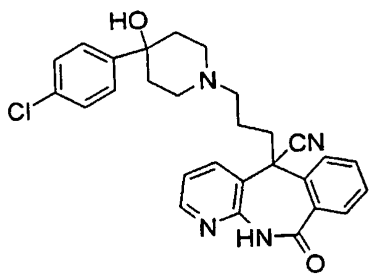
Figure 6P



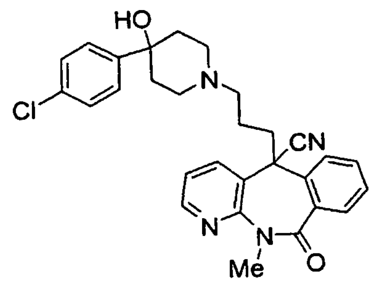
Example 166



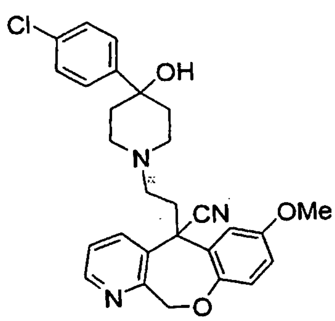
Example 167



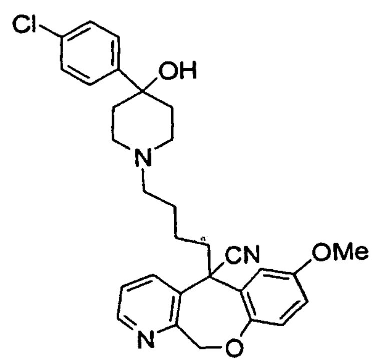
Example 168



Example 169

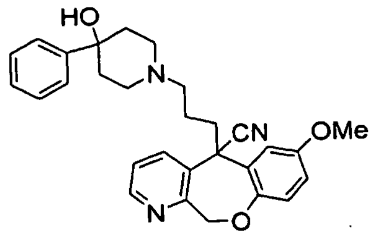


Example 170

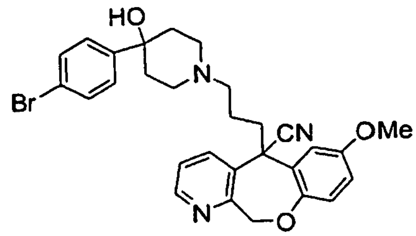


Example 171

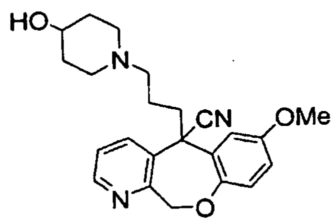
Figure 6Q



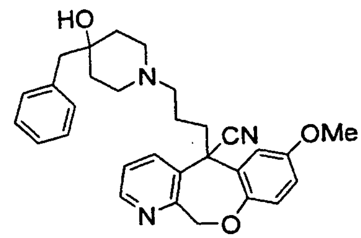
Example 172



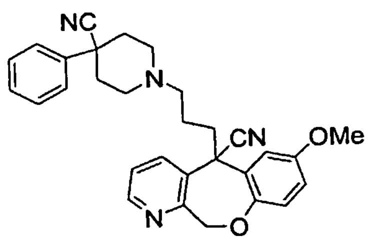
Example 173



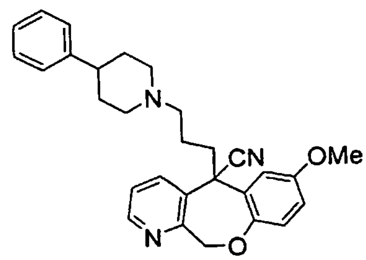
Example 174



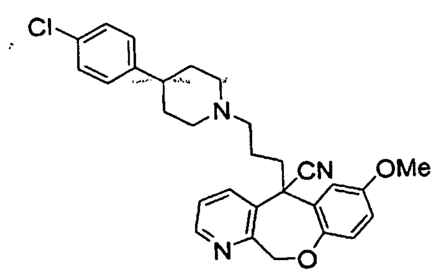
Example 175



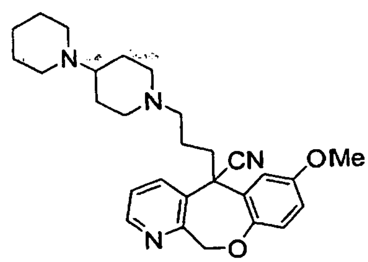
Example 176



Example 177

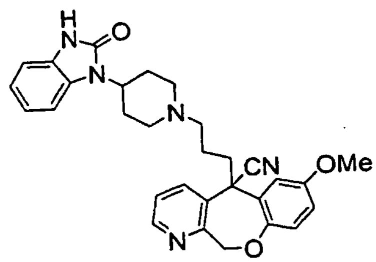


Example 178

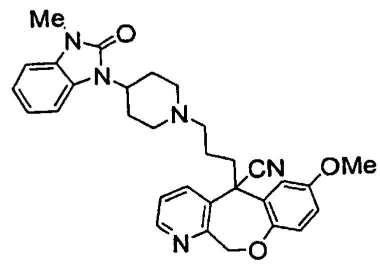


Example 179

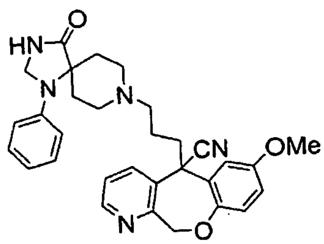
Figure 6R



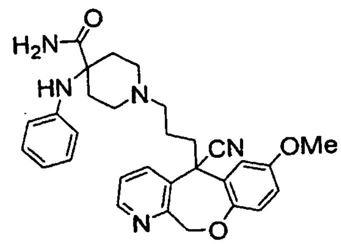
Example 180



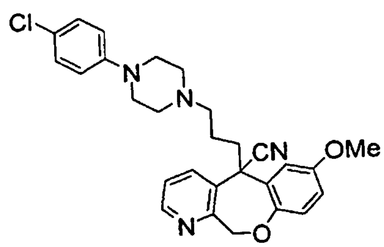
Example 181



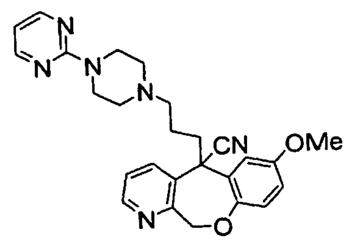
Example 182



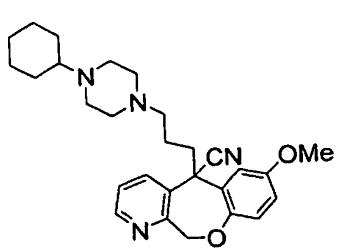
Example 183



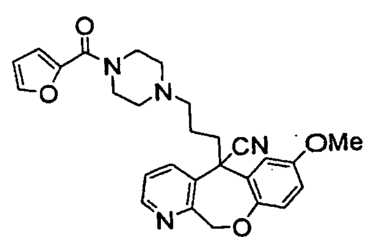
Example 184



Example 185

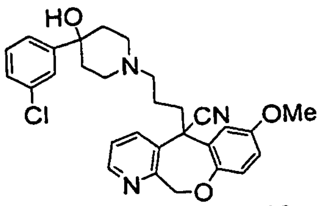


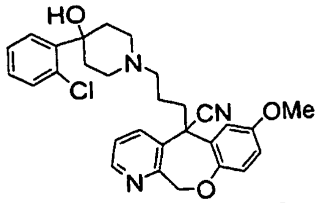
Example 186

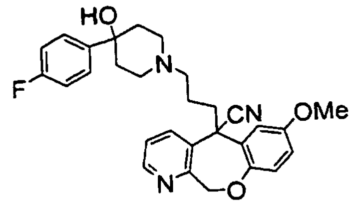


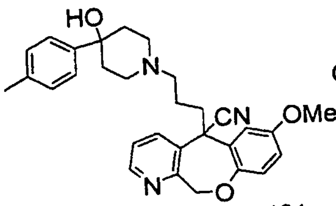
Example 187

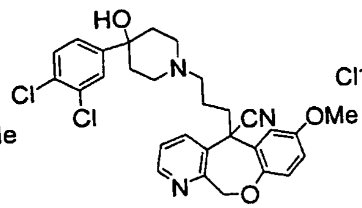
Figure 6S

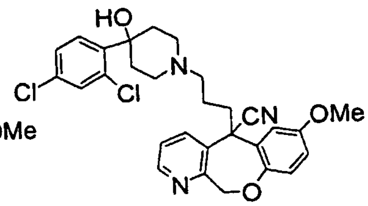

Example 188

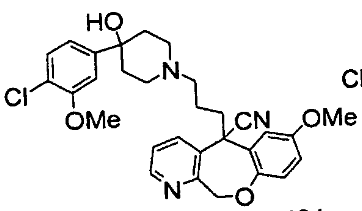

Example 189

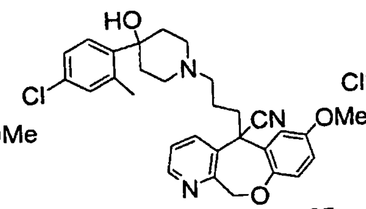

Example 190

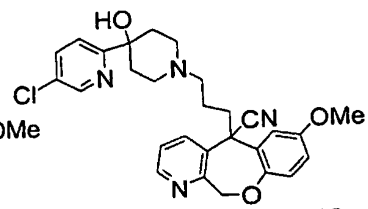

Example 191

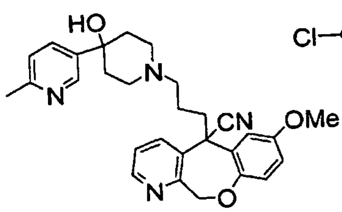

Example 192

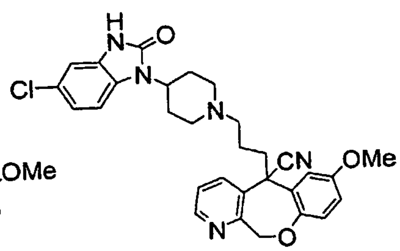

Example 193

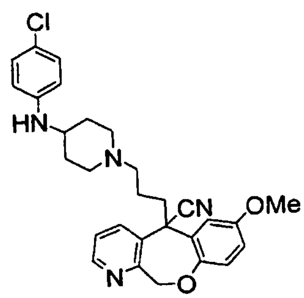

Example 194

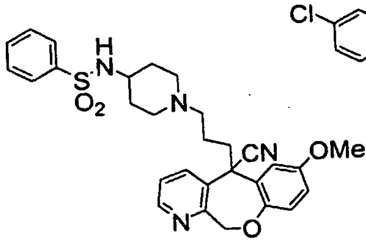

Example 195

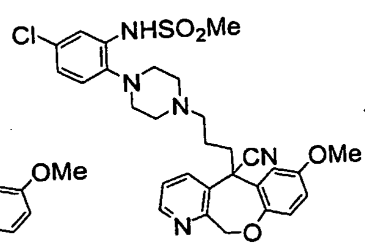

Example 196


Example 197


Example 198


Example 199


Example 200


Example 201

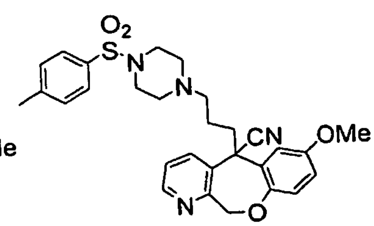
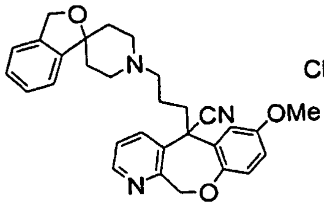
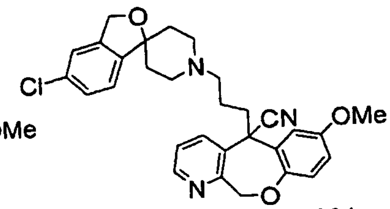
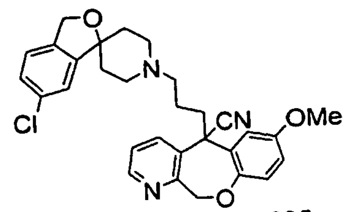
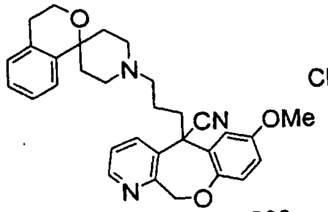

Example 202

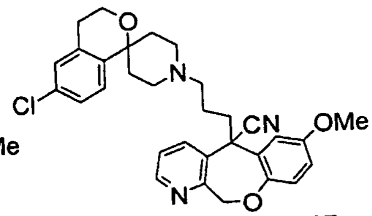
Figure 6T

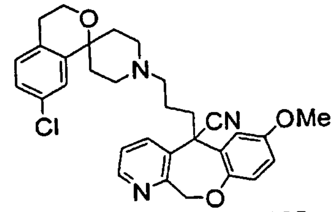

Example 203

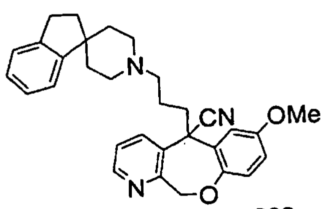

Example 204

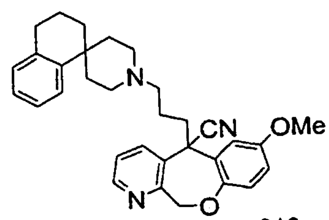

Example 205

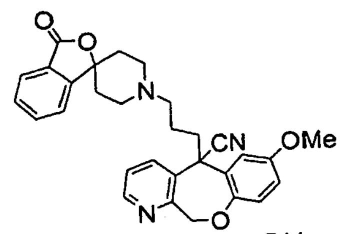

Example 206

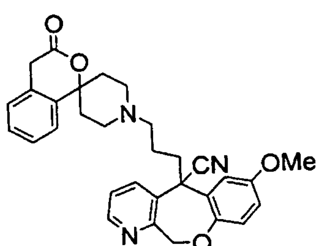

Example 207

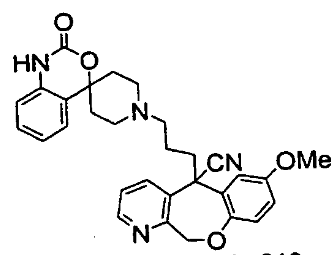

Example 208

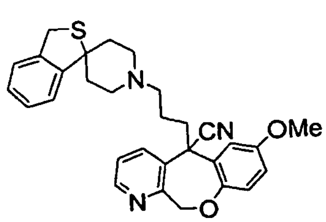

Example 209


Example 210


Example 211


Example 212


Example 213


Example 214

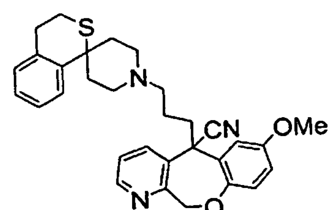
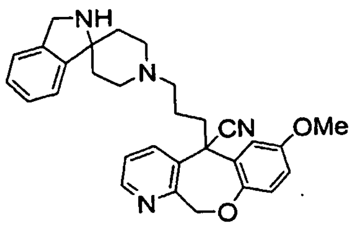
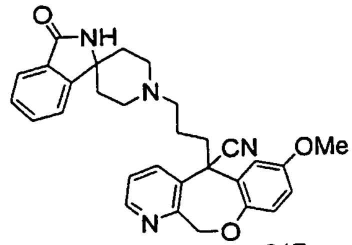

Example 215

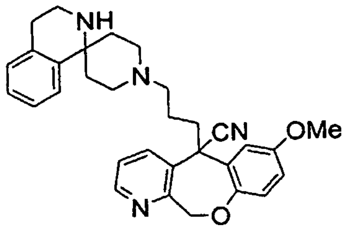
Figure 6U



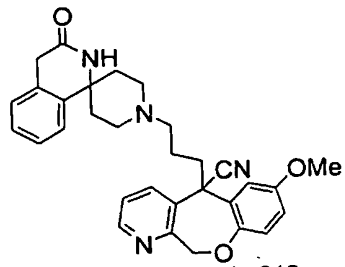
Example 216



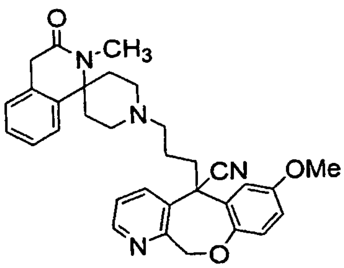
Example 217



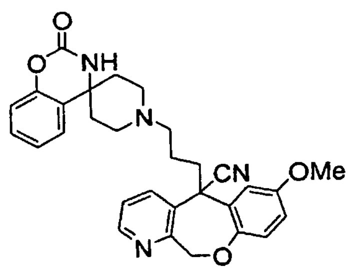
Example 218



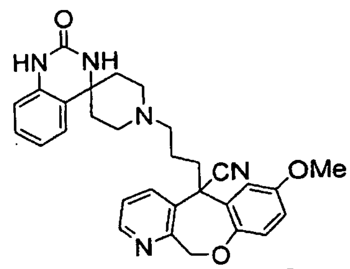
Example 219



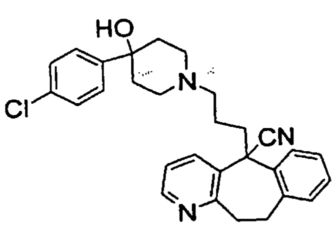
Example 220



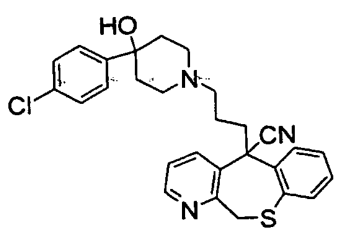
Example 221



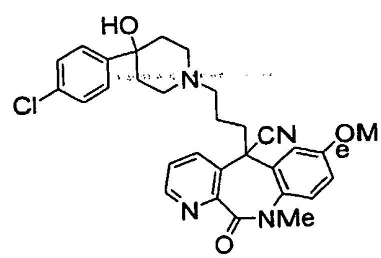
Example 222



Example 223

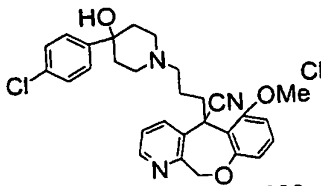


Example 224

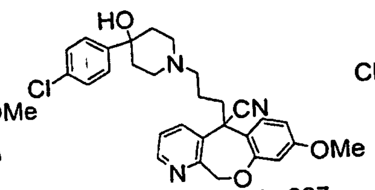


Example 225

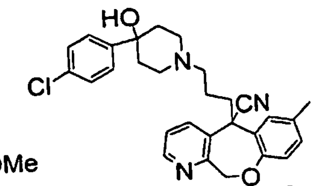
Figure 6V



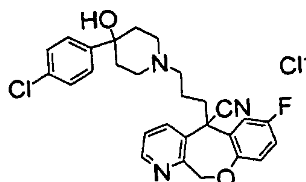
Example 226



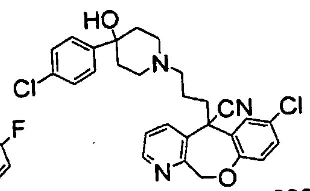
Example 227



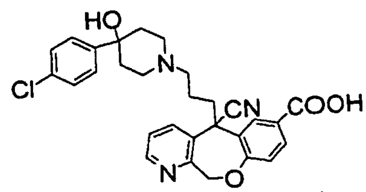
Example 228



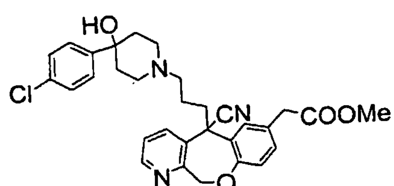
Example 229



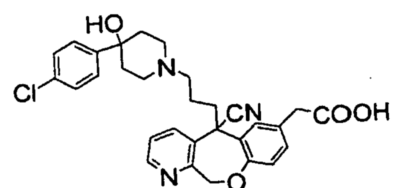
Example 230



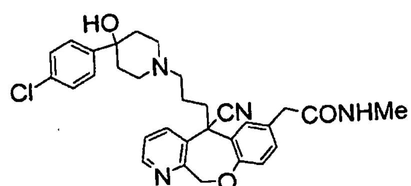
Example 231



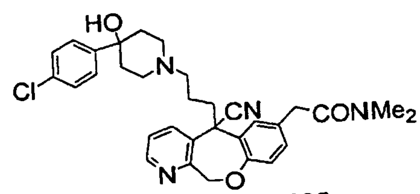
Example 232



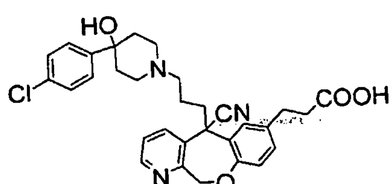
Example 233



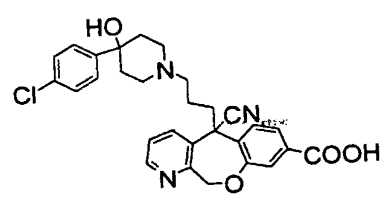
Example 234



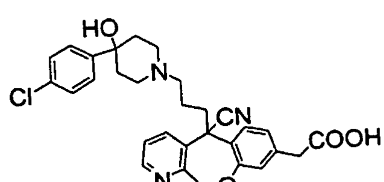
Example 235



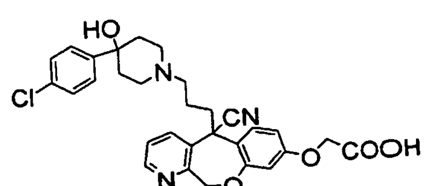
Example 236



Example 237

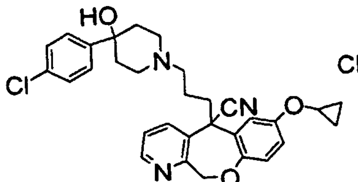


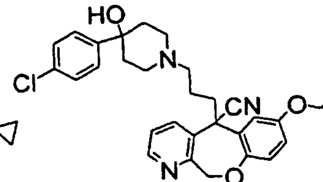
Example 238

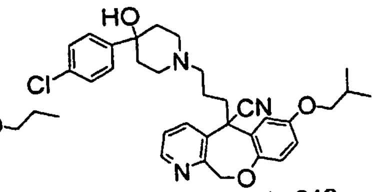


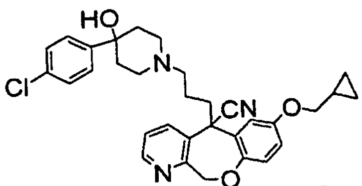
Example 239

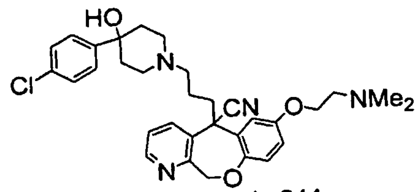
Figure 6W

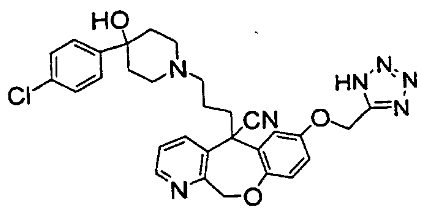

Example 240

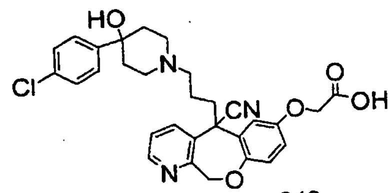

Example 241

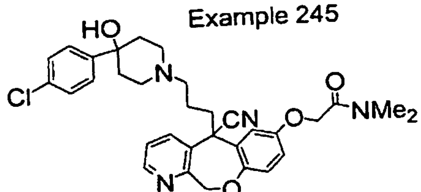

Example 242

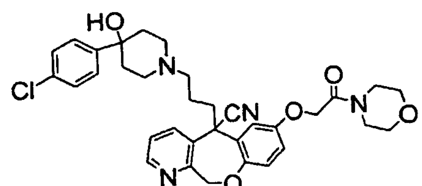

Example 243

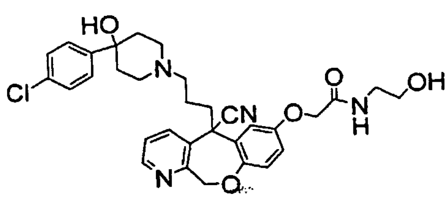

Example 244

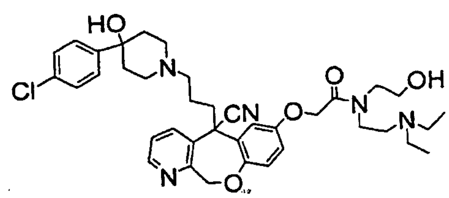

Example 245

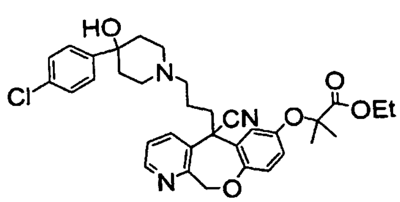

Example 246


Example 247


Example 248


Example 249


Example 250


Example 251

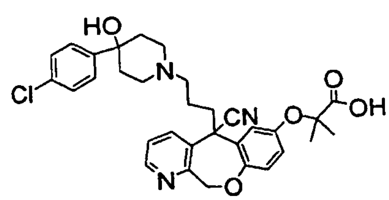
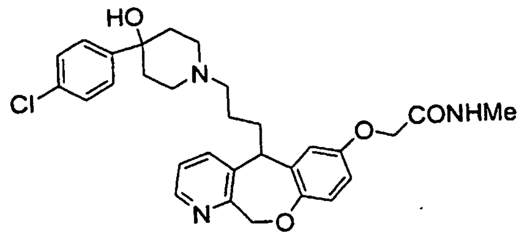
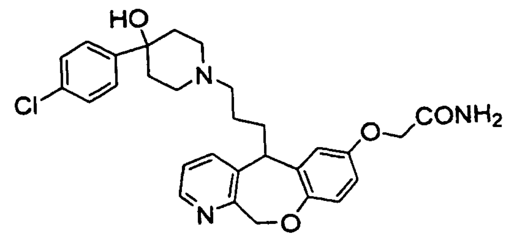

Example 252

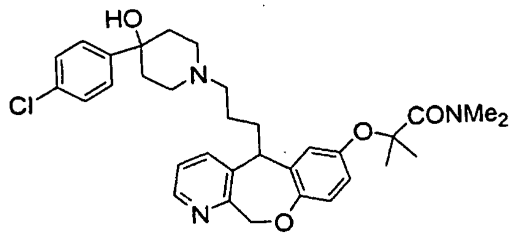
Figure 6X



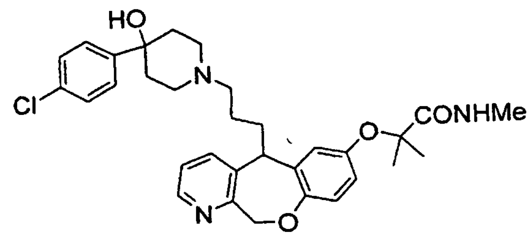
Example 253



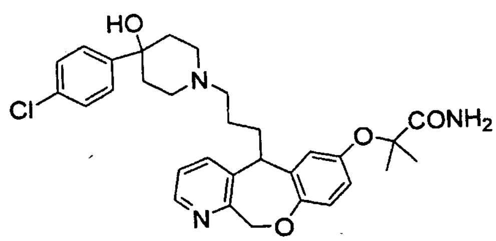
Example 254



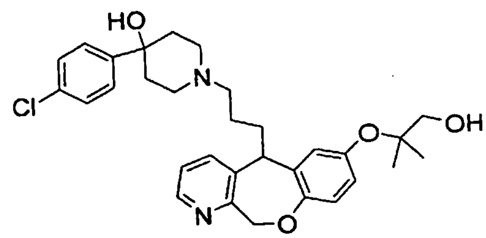
Example 255



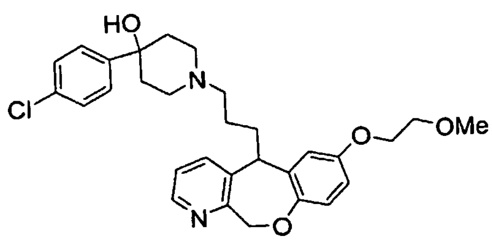
Example 256



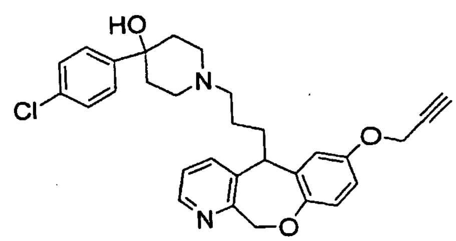
Example 257



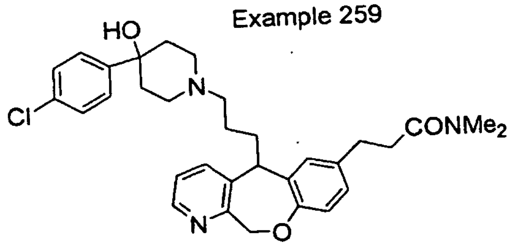
Example 258



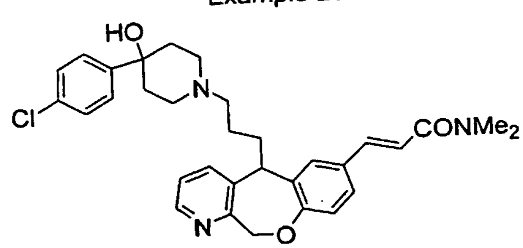
Example 259



Example 260

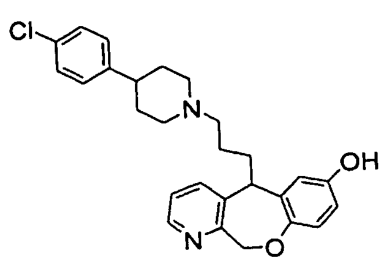


Example 261

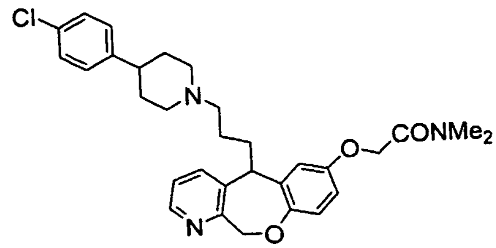


Example 262

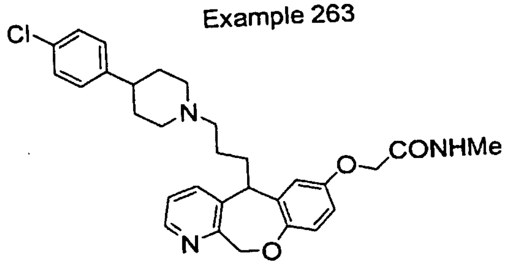
Figure 6Y



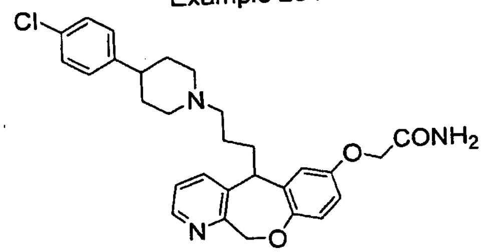
Example 263



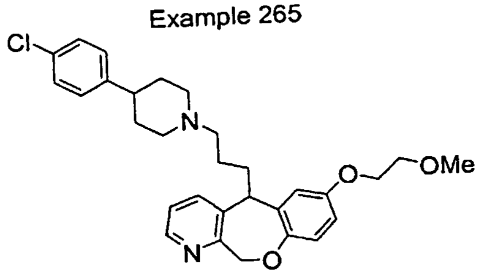
Example 264



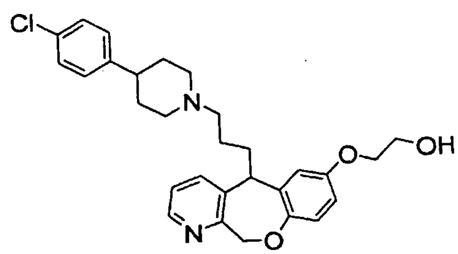
Example 265



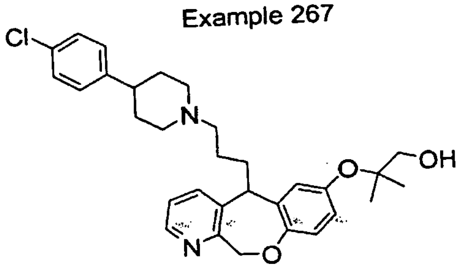
Example 266



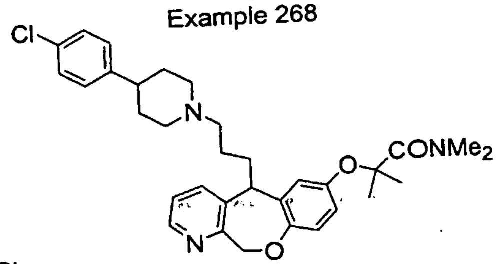
Example 267



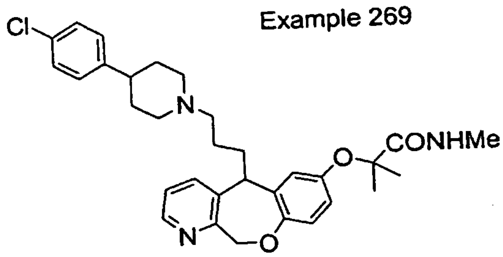
Example 268



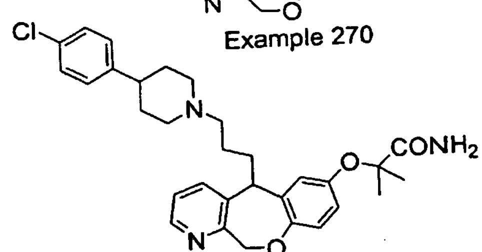
Example 269



Example 270

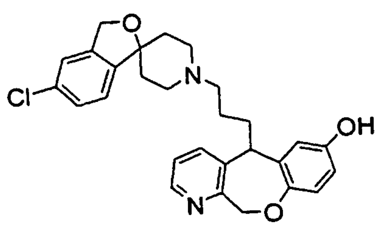


Example 271

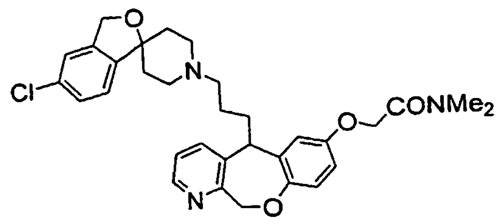


Example 272

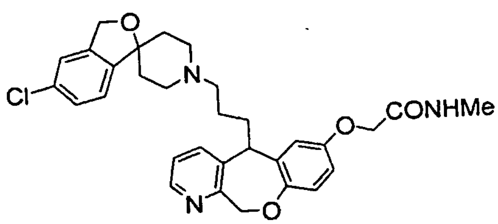
Figure 6Z



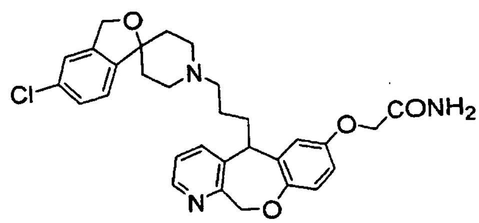
Example 273



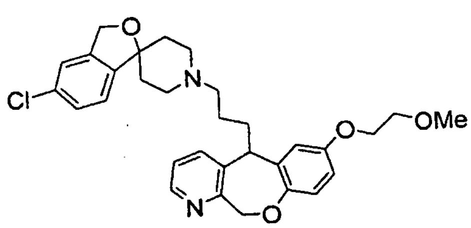
Example 274



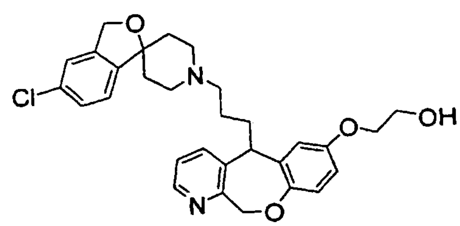
Example 275



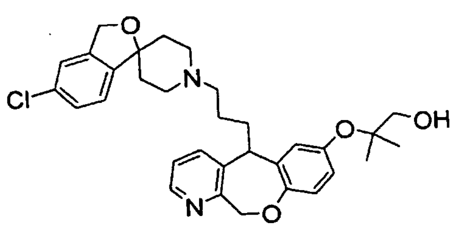
Example 276



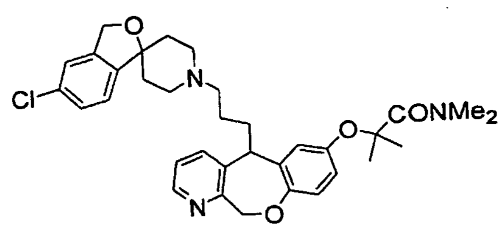
Example 277



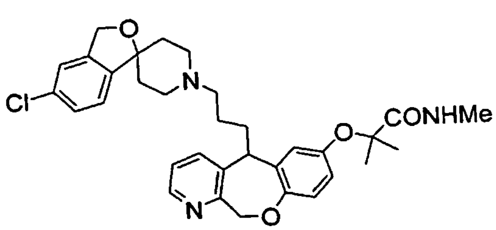
Example 278



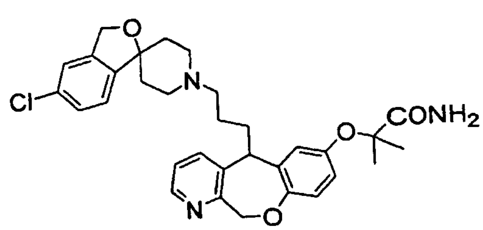
Example 279



Example 280

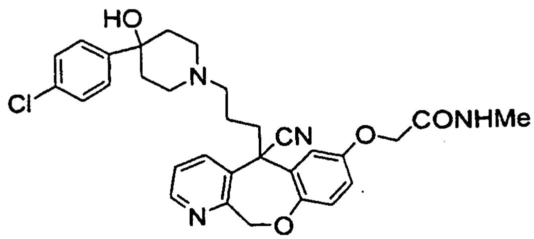


Example 281

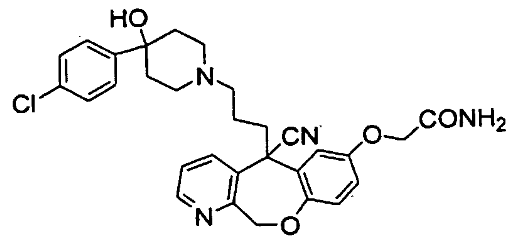


Example 282

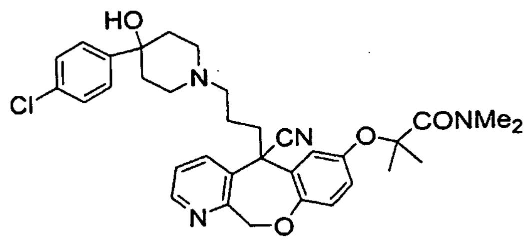
Figure 6AA



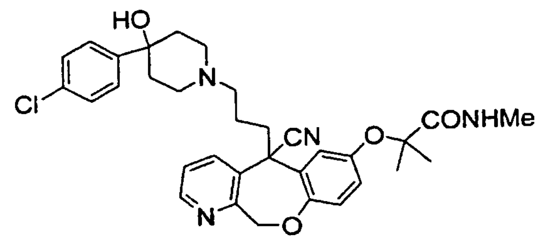
Example 283



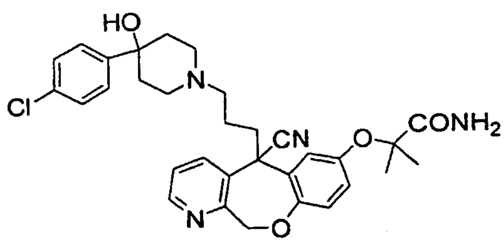
Example 284



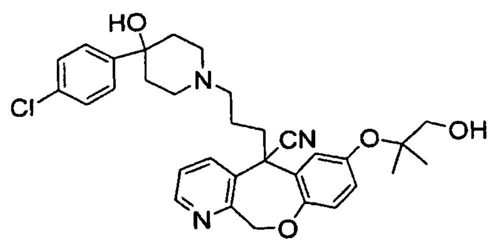
Example 285



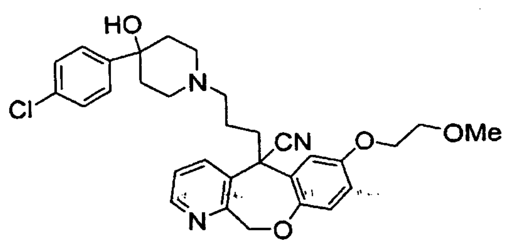
Example 286



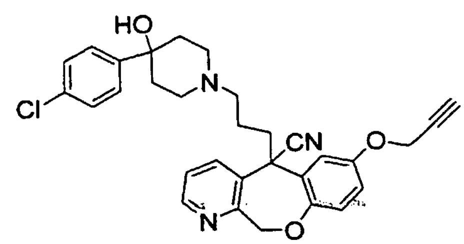
Example 287



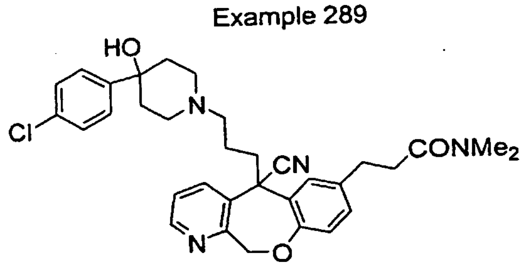
Example 288



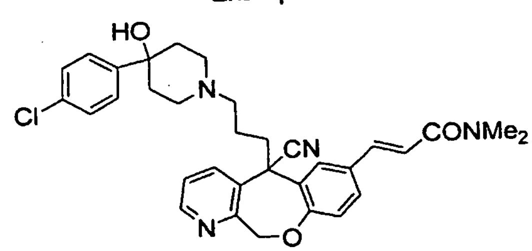
Example 289



Example 290

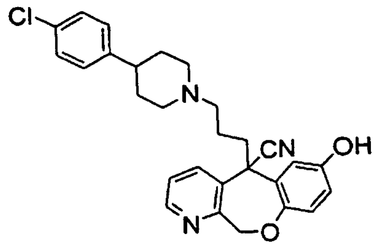


Example 291

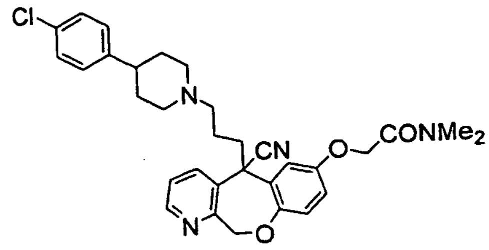


Example 292

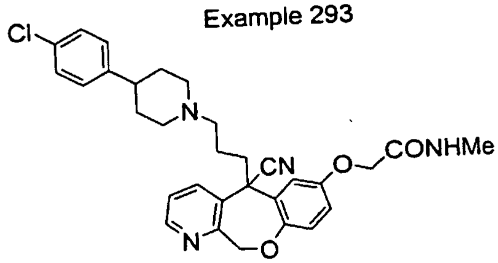
Figure 6AB



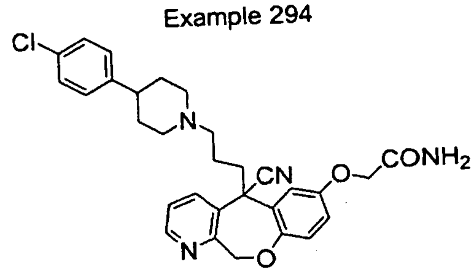
Example 293



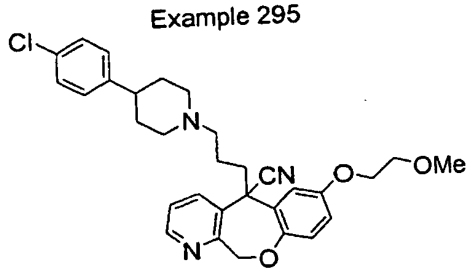
Example 294



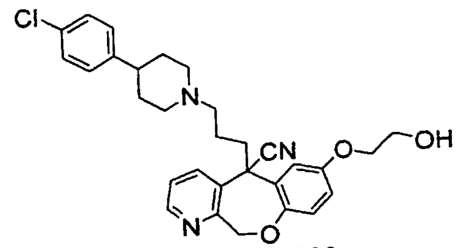
Example 295



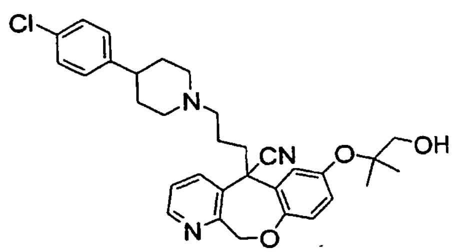
Example 296



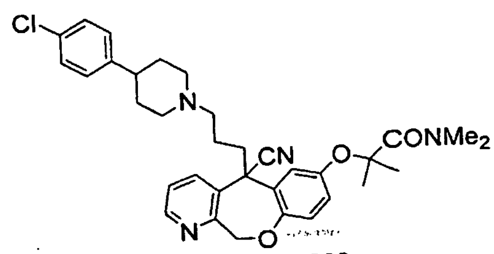
Example 297



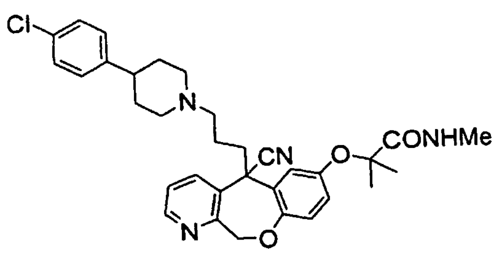
Example 298



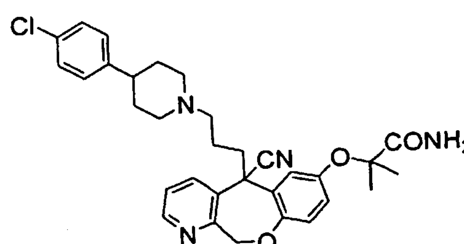
Example 299



Example 300

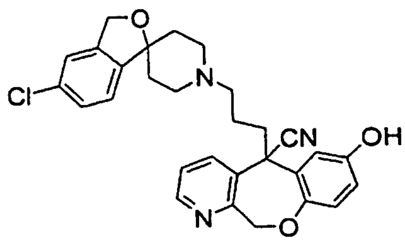


Example 301

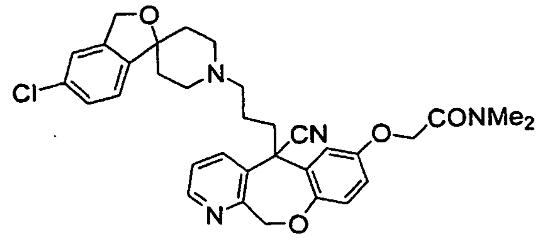


Example 302

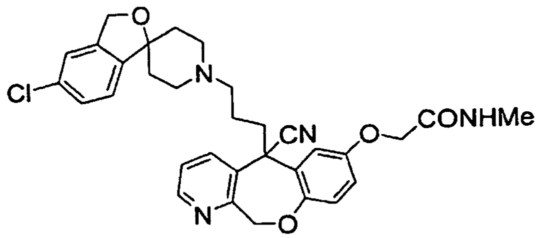
Figure 6AC



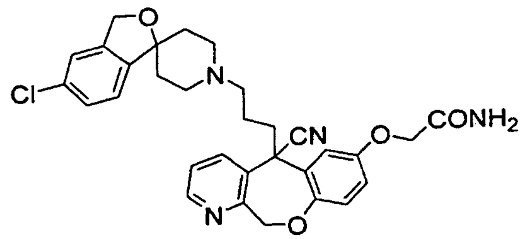
Example 303



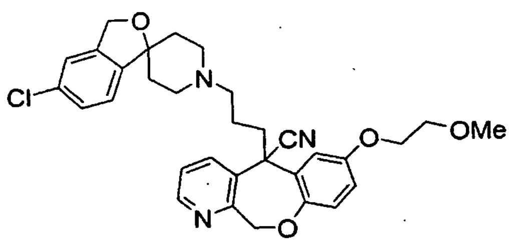
Example 304



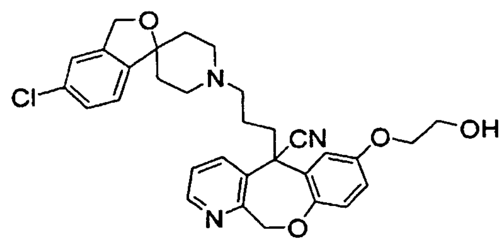
Example 305



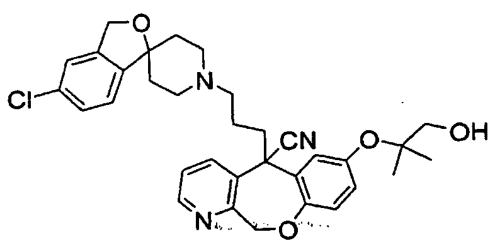
Example 306



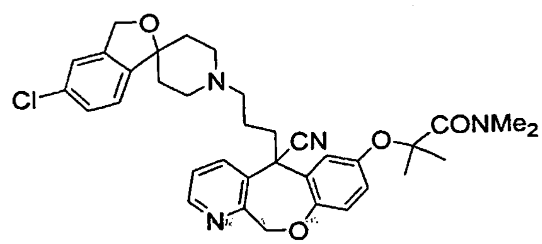
Example 307



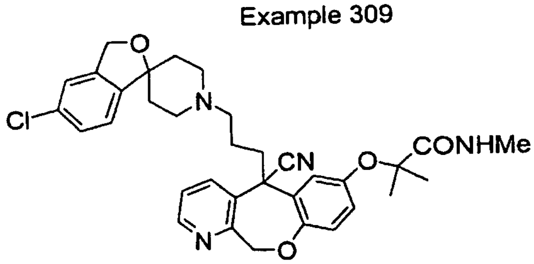
Example 308



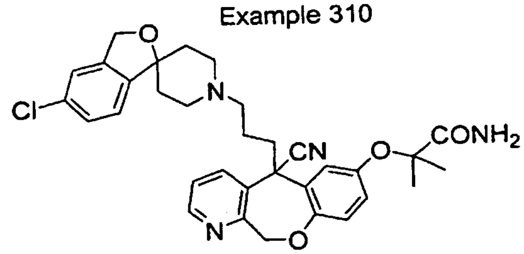
Example 309



Example 310



Example 311



Example 312

Figure 6AD

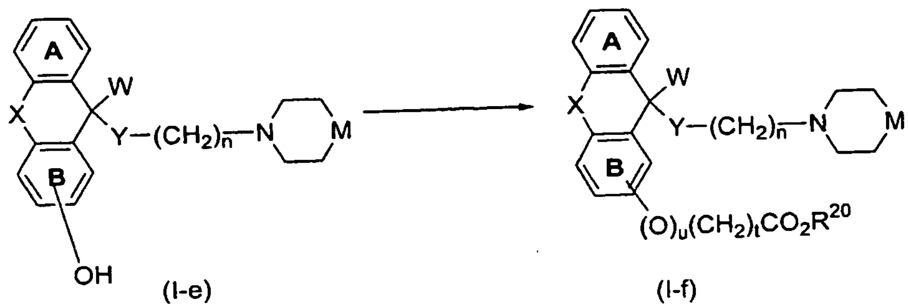
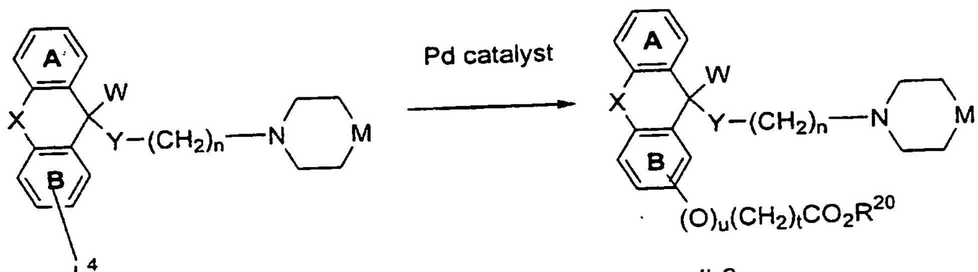


Figure 7



(I-e) (I-f)

Figure 8A

Fig.8b

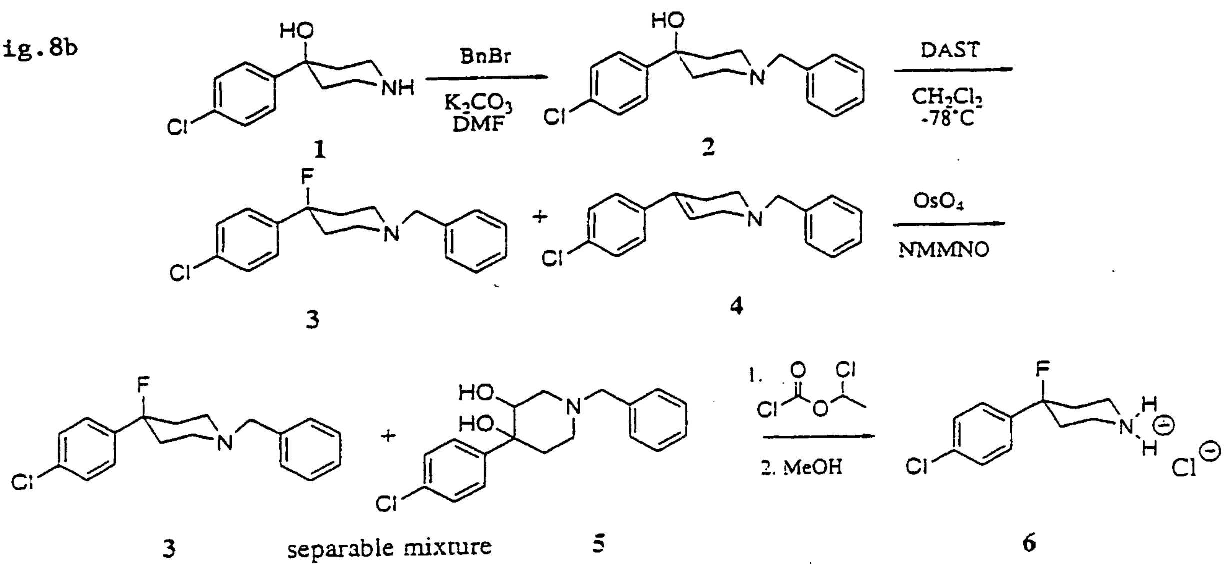


Fig.8c

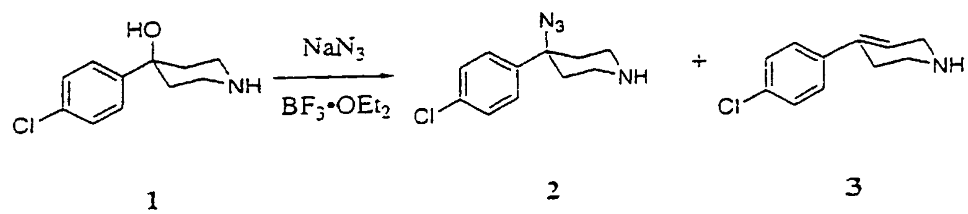


Fig.8d

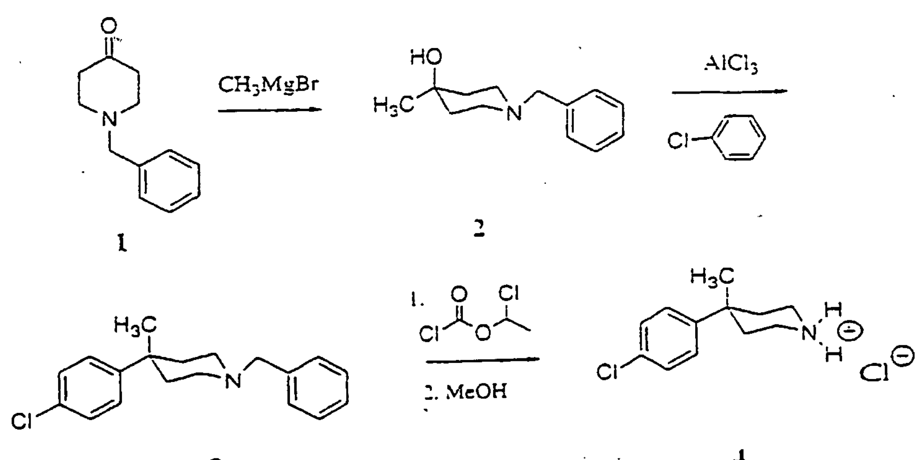
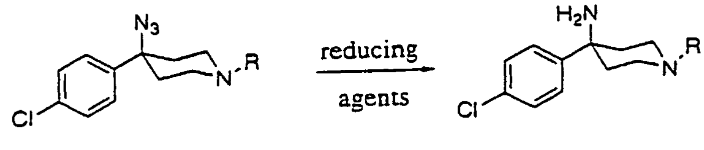


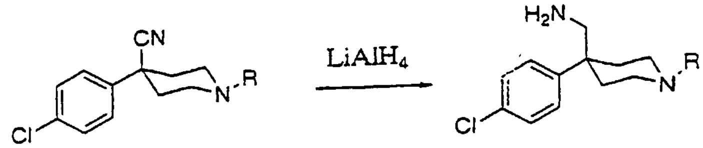
Fig. 9a



1

2

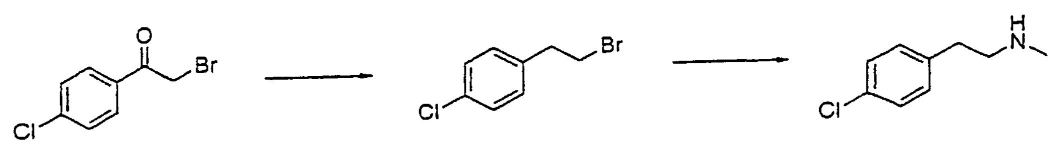
Fig. 9b



1

2

Fig. 9c

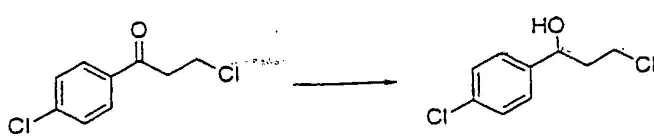


1

2

3

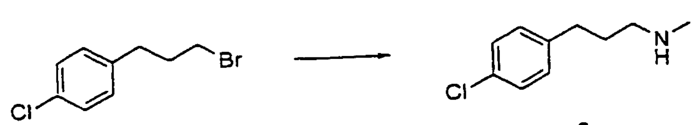
Fig. 9d



1

2

Fig. 9e



1

2

Figure 10a

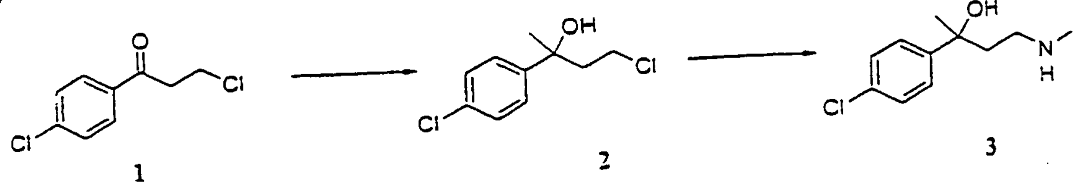


Figure 10b

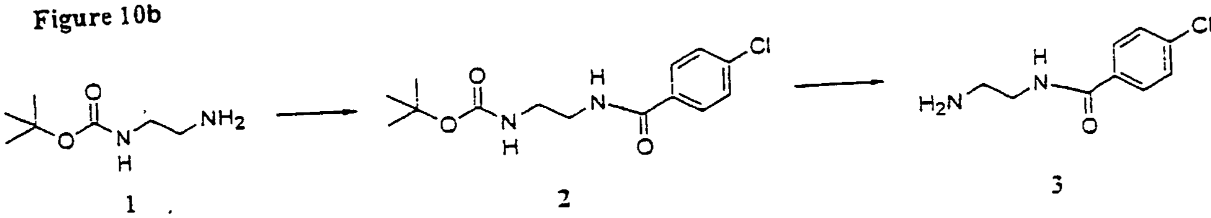


Figure 10c

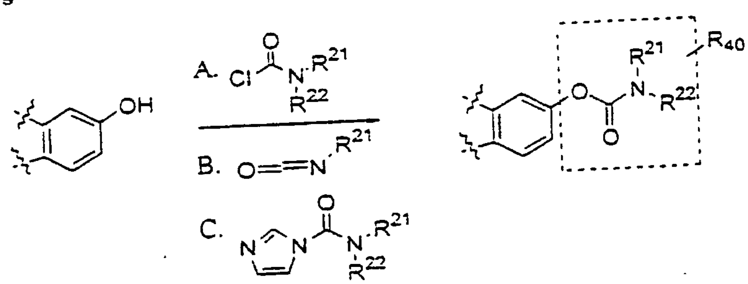
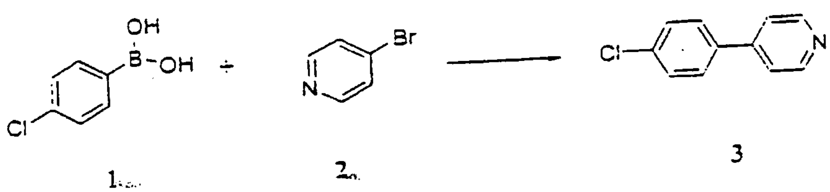
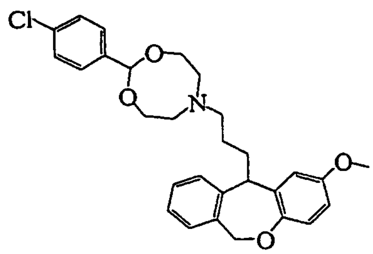
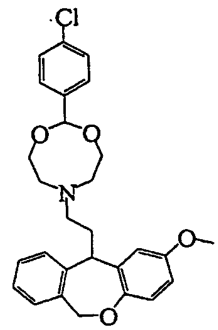


Figure 10 d

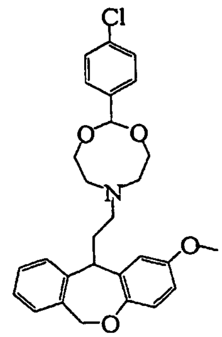




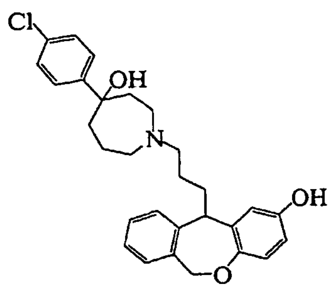
Example 313



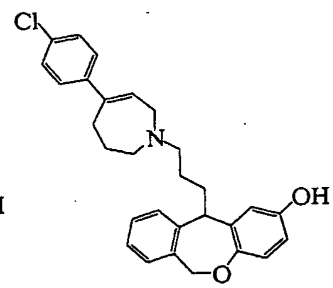
Example 314



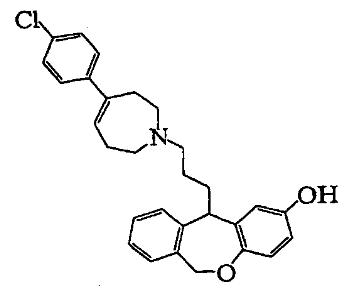
Example 315



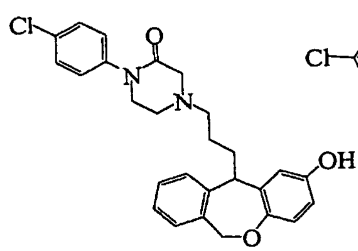
Example 316



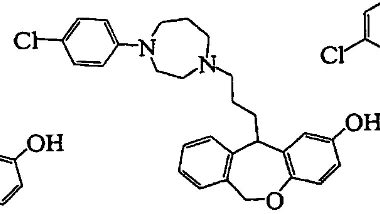
Example 317



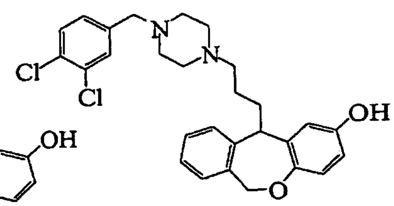
Example 318



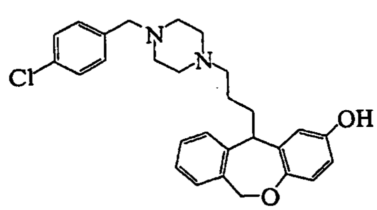
Example 319



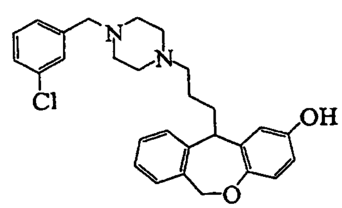
Example 320



Example 321

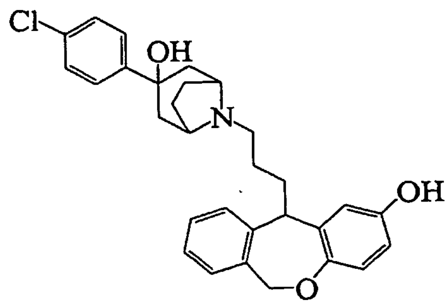


Example 322

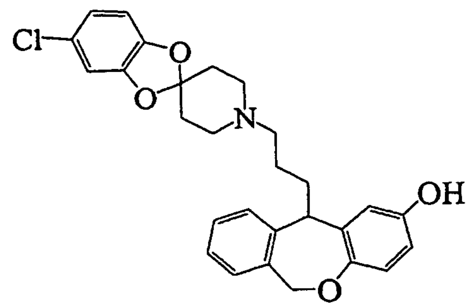


Example 323

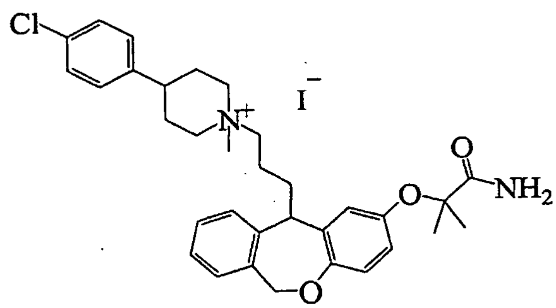
Figure 11A



Example 324

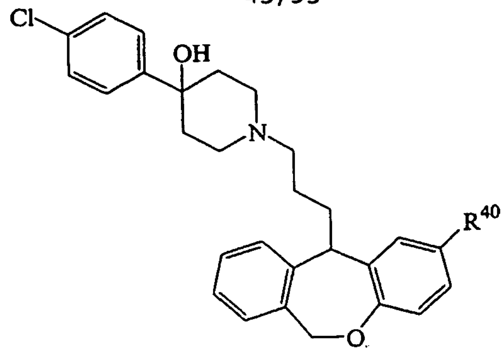


Example 325

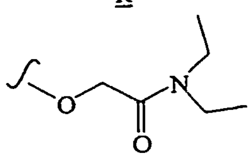


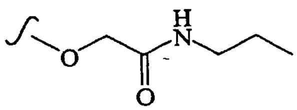
Example 326

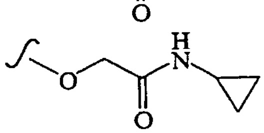
Figure 11B

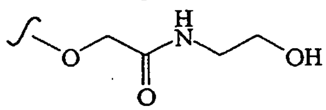


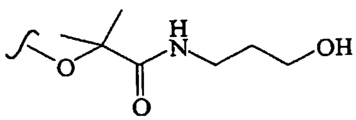
$\underline{R^{40}}$

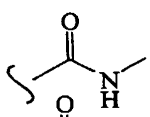
Example 327 

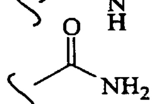
Example 328 

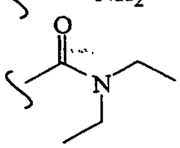
Example 329 

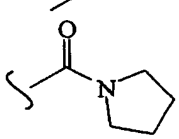
Example 330 

Example 331 

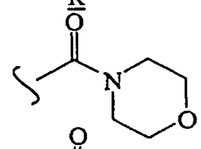
Example 332 

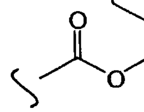
Example 333 

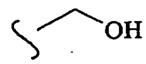
Example 334 

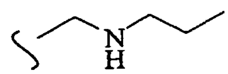
Example 335 

$\underline{R^{40}}$

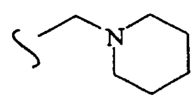
Example 336 

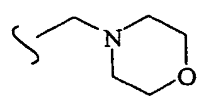
Example 337 

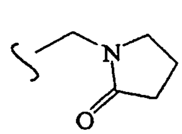
Example 338 

Example 339 

Example 340 

Example 341 

Example 342 

Example 343 

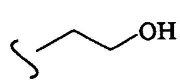
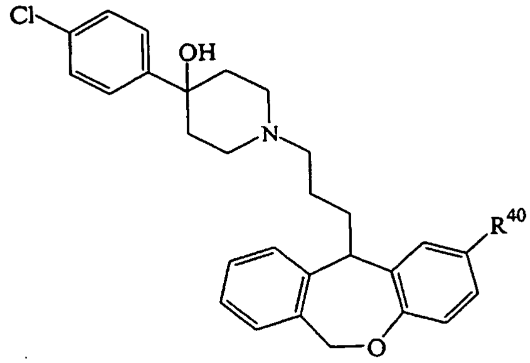
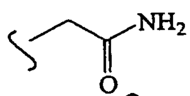
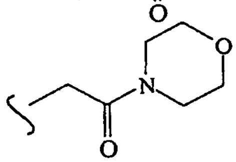
Example 344 

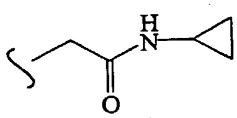
Figure 11C

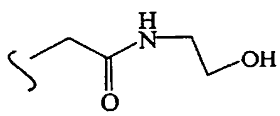


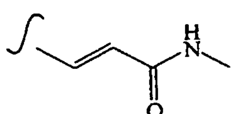
R40

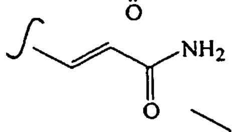
Example 345 

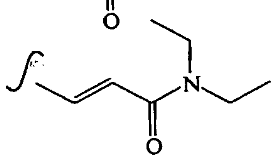
Example 346 

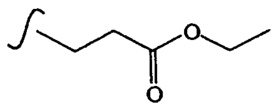
Example 347 

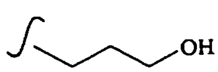
Example 348 

Example 349 

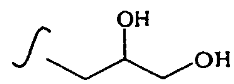
Example 350 

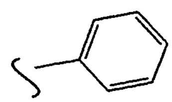
Example 351 

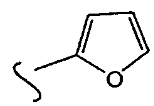
Example 352 

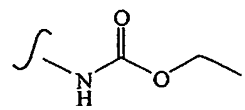
Example 353 

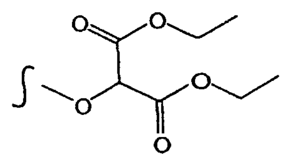
R40

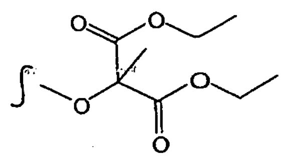
Example 354 

Example 355 

Example 356 

Example 357 

Example 358 

Example 359 

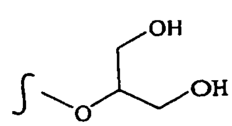
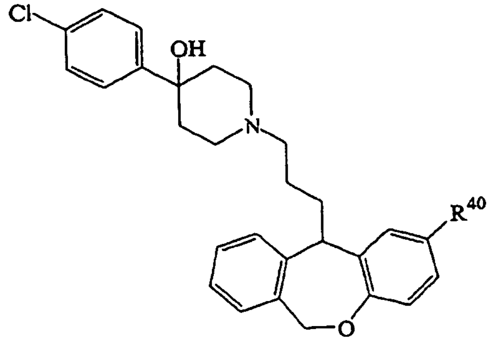
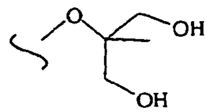
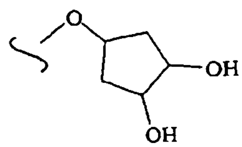
Example 360 

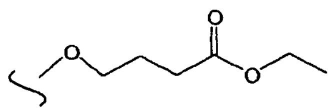
Figure 11D

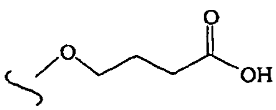


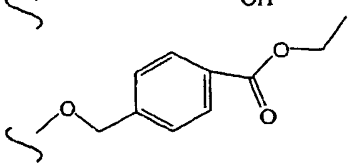
R40

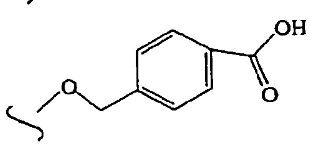
Example 361


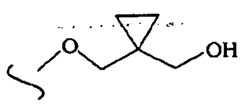
Example 362


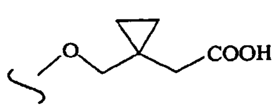
Example 363


Example 364


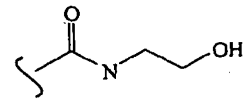
Example 365


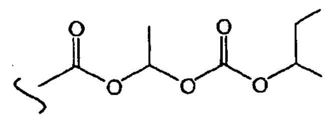
Example 366


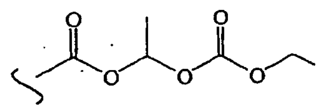
Example 367


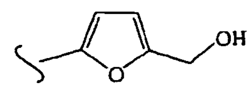
Example 368


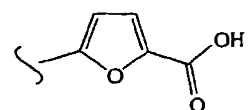
R40

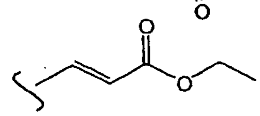
Example 369


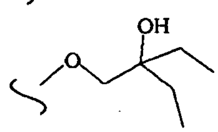
Example 370


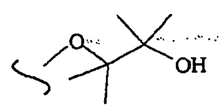
Example 371


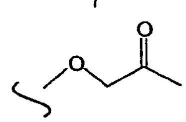
Example 372


Example 373


Example 374


Example 375


Example 376


Example 377


Example 378 -CHO

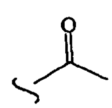
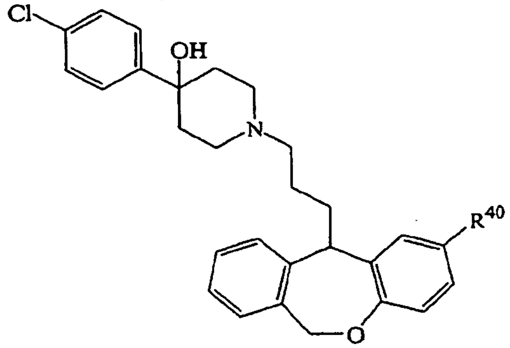
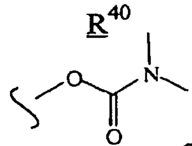
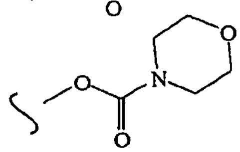
Example 379


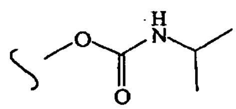
Figure 11E

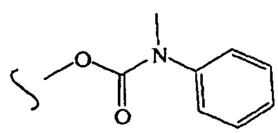


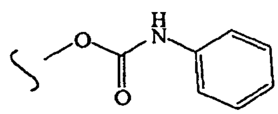
$\underline{R^{40}}$

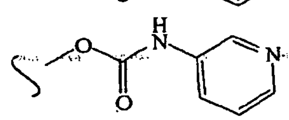
Example 380 

Example 381 

Example 382 

Example 383 

Example 384 

Example 385 

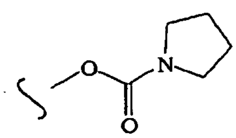
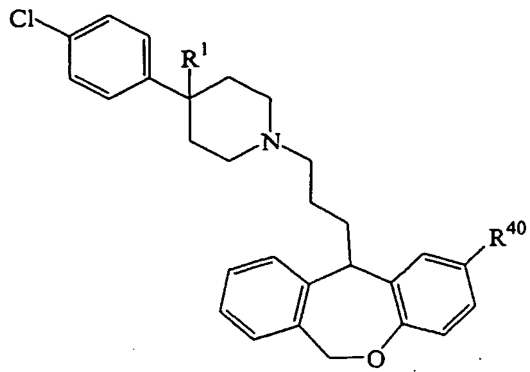
Example 386 

Figure 11F



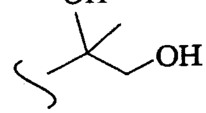
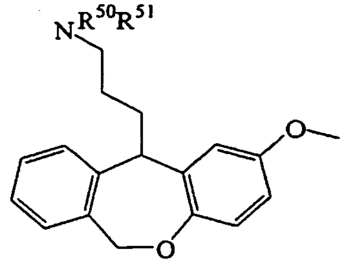
	$\underline{R}^1$	$\underline{R}^{40}$
Example 387	-CN	$-OCH_3$
Example 388	$-CH_2NH_2$	$-OCH_3$
Example 389	$-NH_2$	$-OCH_3$
Example 390	$-CH_3$	$-OCH_3$
Example 391	$-OCH_3$	$-OCH_3$
Example 392	-F	-OH
Example 393	$-CH_3$	-OH
Example 394	$-CH_3$	

Figure 11G



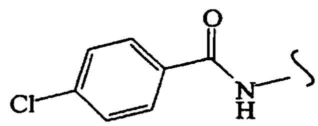
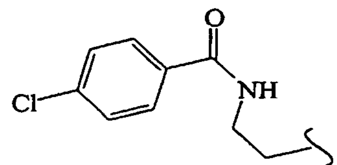
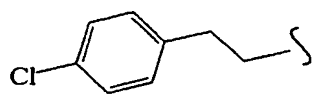
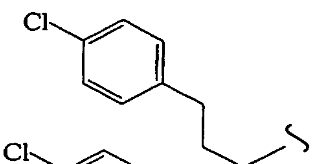
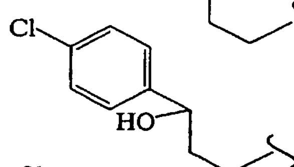
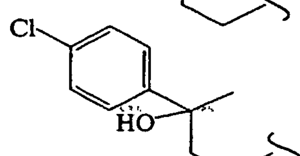
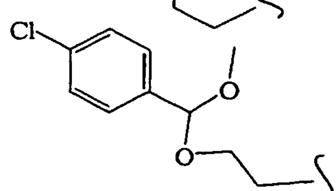
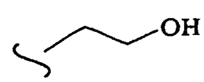
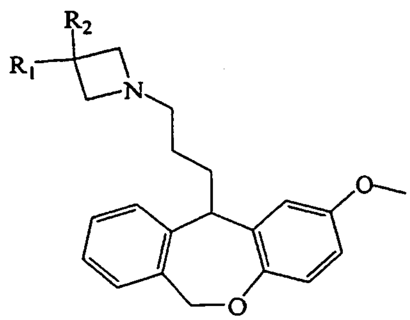
	R50	R51
Example 395		-H
Example 396		-H
Example 397		$-CH_3$
Example 398		$-CH_3$
Example 399		$-CH_3$
Example 400		$-CH_3$
Example 401		

Figure 11H



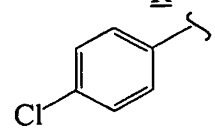
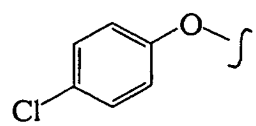
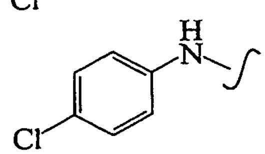
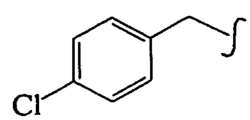
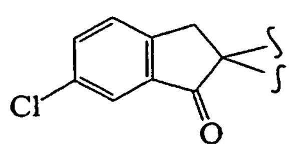
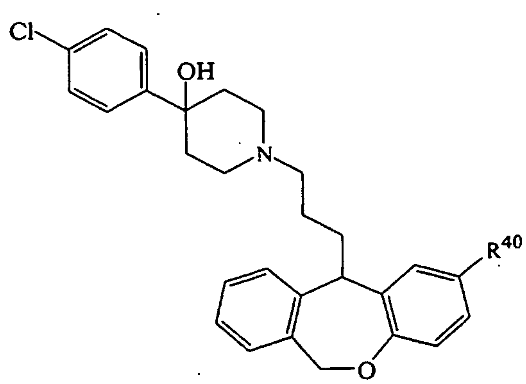
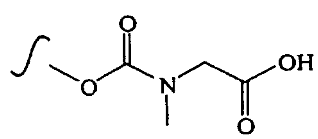
	$\underline{R}^1$	$\underline{R}^2$
Example 402	-OH	
Example 403	-H	
Example 404	-H	
Example 405	-OH	
Example 406		

Figure 11I



R^{40}

Example 407 

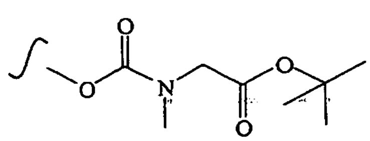
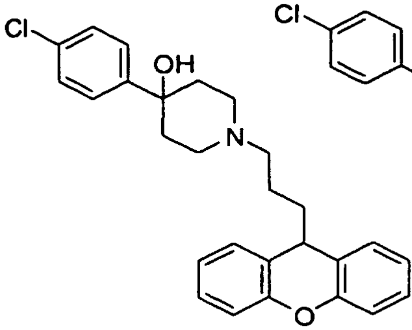
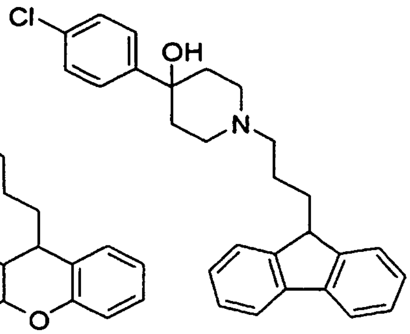
Example 408 

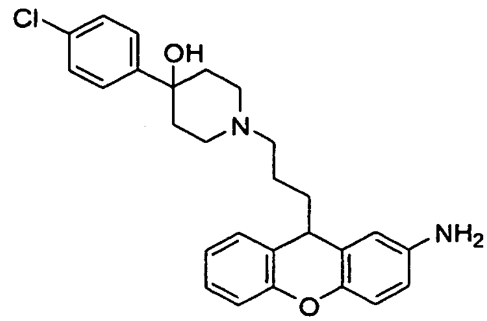
Figure 11J



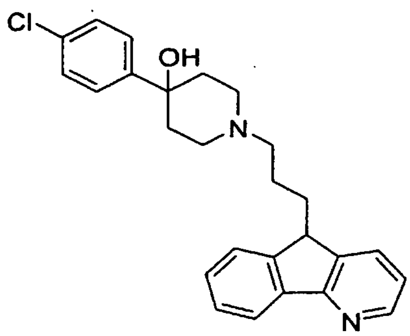
Example 409



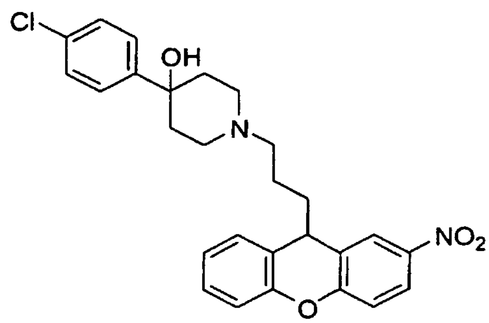
Example 410



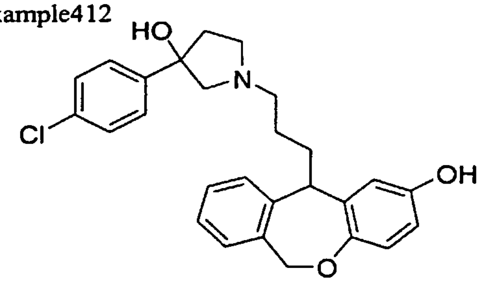
Example411



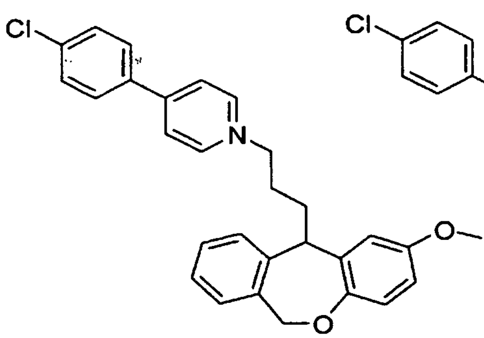
Example412



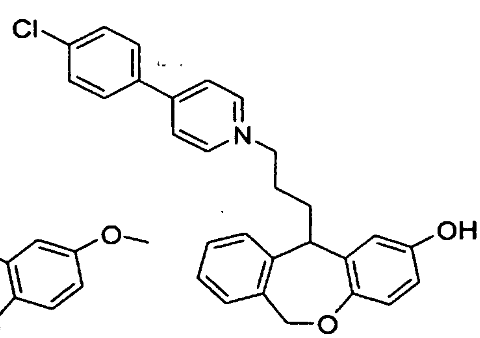
Example 413



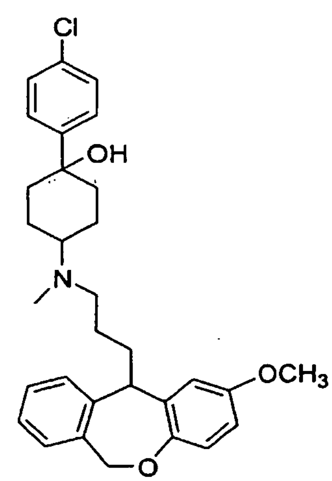
Example 414



Example 415

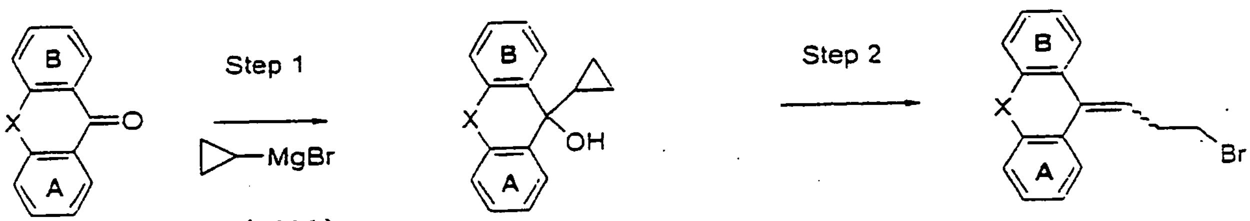


Example 416



Example 417

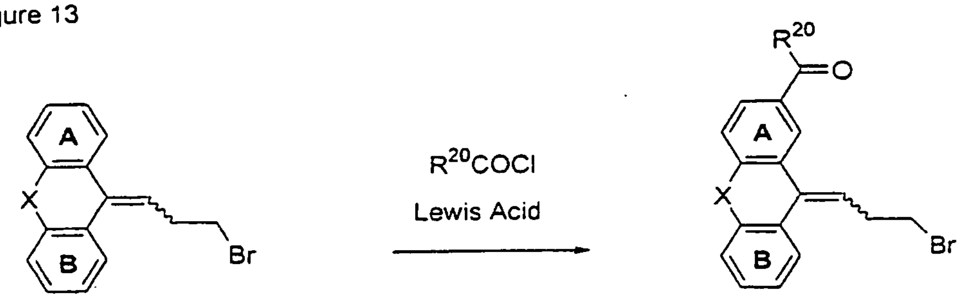
Figure 11K



(II) (X111) (XIV) (XV-b)

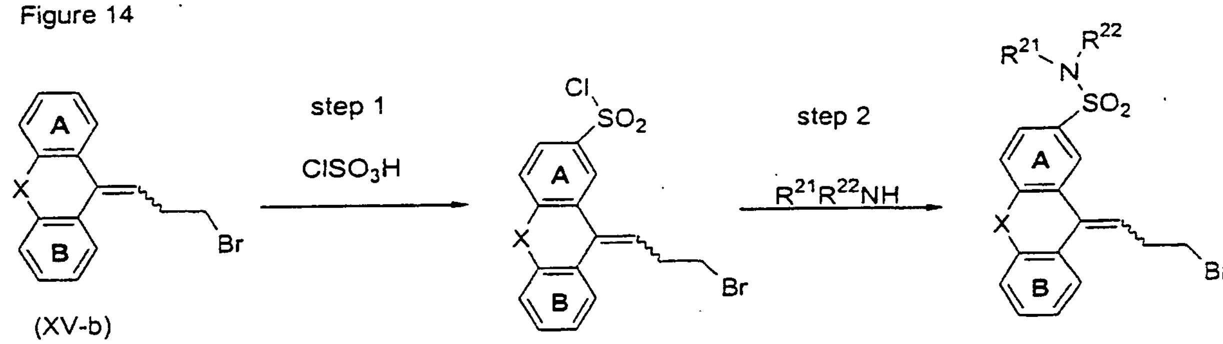
Figure 12

Figure 13



(XV-b) (XV-c)

Figure 14



(XV-b) (XV-d) (XV-e)